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(54) Title: TRANSABDOMINAL EXAMINATION, MONITORING AND IMAGING OF TISSUE

(57) Abstract

An optical examination technique employs an optical system (15, 45, 100, 150, 200, 260 or 300) for *in vivo*, non–invasive examination of internal tissue of a subject. The optical system includes an optical module (12 or 14), a controller and a processor. The optical module is arranged for placement on the exterior of the abdomen or chest. The module includes an array of optical input ports and optical detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths targeted to examine a selected tissue region, such as an internal organ or an in utero fetus. Each optical input port is constructed to introduce into the examined tissue visible or infrared light emitted from a light source. Each optical detection port is constructed to provide light from the tissue to a light detector. The controller is constructed and arranged to activate one or several light sources and light detectors so that the light detector detects light that has migrated over at least one of the photon migration paths. The processor receives signals corresponding to the detected light and forms at least one data set used for tissue examination.

TRANSABDOMINAL EXAMINATION, MONITORING AND IMAGING OF TISSUE

This application claims priority from U.S. Provisional Application Serial No. 60/074,642 filed on February 13, 1998, U.S. Provisional Application Serial No. 60/098,172 filed on August 26, 1998, and U.S. Provisional Application Serial No. 60/098,018 filed on August 26, 1998, all of which are incorporated by reference as if fully set forth herein.

The Field of the Invention

The present invention relates to non-invasive, *in-vivo* examination, imaging and characterization of biological tissue using visible or infra-red radiation, and more particularly to transabdominal or transthoracic non-invasive examination, monitoring and imaging of internal tissue or an in utero fetus.

Background

Traditionally, X-rays or γ-rays has been used to examine and image biological tissue. This radiation propagates in the tissue on straight, ballistic tracks, i.e., scattering of the radiation is negligible. Thus, imaging is based on evaluation of the absorption levels of different tissue types. For example, in roentgenography the X-ray film contains darker and lighter spots. In more complicated systems, such as computerized tomography (CT), a cross-sectional picture of human organs is created by transmitting X-ray radiation through a section of the human body at different angles and by electronically detecting the variation in X-ray transmission. The detected intensity information is digitally stored in a computer which reconstructs the X-ray absorption of the tissue at a multiplicity of points located in one cross-sectional plane.

Near infra-red radiation (NIR) has been used to study non-invasively the oxygen metabolism in tissue (for example, the brain, finger, or ear lobe). Using visible, NIR and infra-red (IR) radiation for medical imaging could bring several advantages. In the NIR or IR range the contrast factor between a tumor and a tissue is much larger than in the X-ray range. In addition, the visible to IR radiation is preferred over the X-ray radiation since it is non-ionizing and thus, potentially causes fewer side effects. However, the visible or IR radiation is strongly scattered and absorbed in biological tissue, and the migration path cannot be approximated by a straight line, making inapplicable certain aspects of cross-sectional imaging techniques.

Computerized Tomography using NIR spectrometry has been used for *in vivo* imaging. This technique utilizes NIR radiation in an analogous way to the use of X-ray radiation in an X-

ray CT. The X-ray source is replaced by several laser diodes emitting light in the NIR range.
The NIR-CT uses a set of photodetectors that detect the light of the laser diodes transmitted
through the imaged tissue. The detected data are manipulated by a computer similarly as the
detected X-ray data would be in an X-ray CT. Different NIR-CT systems have recognized the
scattering aspect of the non-ionizing radiation and have modified the X-ray CT algorithms
accordingly.

The above-mentioned X-ray or γ-ray techniques have been used to detect a tissue tumor.
Under the term "angiogenesis" I mean the generation of new blood vessels into a tissue or organ.
Under normal physiological conditions humans or animals undergo angiogenesis only in very
specific restricted situations. For example, angiogenesis is normally observed in wound healing,
fetal and embryonal development and formation of the corpus luteum, endometrium and
placenta.

Both controlled and uncontrolled angiogenesis are thought to proceed in a similar
manner. Persistent, unregulated angiogenesis occurs in a multiplicity of disease states, tumor
metastasis and abnormal growth by endothelial cells and supports the pathological damage seen
in these conditions. The diverse pathological disease states in which unregulated angiogenesis is
present have been grouped together as angiogenic dependent or angiogenic associated diseases.
The hypothesis that tumor growth is angiogenesis dependent was first proposed in 1971.
(Folkman J., Tumor Angiogenesis: Therapeutic Implications., N. Engl. Jour. Med. 285: 1182-
1186, 1971) In its simplest terms it states: "Once tumor 'take' has occurred, every increase in
tumor cell population must be preceded by an increase in new capillaries converging on the
tumor." Tumor 'take' is understood to indicate a prevascular phase of tumor growth in which a
population of tumor cells occupying a few cubic millimeters volume and not exceeding a few
million cells, can survive on existing host microvessels. Expansion of tumor volume beyond this
phase requires the induction of new capillary blood vessels. This explanation was directly or
indirectly observed and documented in numerous publications.

Ultrasound systems are widely used for in utero examination of a fetus. However, these
systems are not very sensitive to tissue oxygenation. Perinatal brain injury, such as hypoxic -
ischemic encephalopathy (HIE) and germinal-matrix intraventricular hemorrhage (GM-IVH), is
still a significant source of neurological morbidity, cerebral palsy (CP), mental retardation, and
seizures. Premature fetuses and infants are particularly at high risk of developing brain injury.
GM-IVH, a common problem related to prematurity, is a potent risk factor for CP. The overall

incidence of CP is approximately 1 to 2 per 1000 live births; however, the incidence dramatically increases with prematurity, i.e. 15 per 1000 live births for those weighing less than 2500g, and from 13 to 90 per 1000 survivors from 500-1500g.

None of the existing diagnostic methods for fetal surveillance provides very accurate information on fetal cerebral hemodynamics and oxygenation. Antepartum electronic fetal heart rate (FHR) monitoring, either alone (non stress test - NST) or as the part of the biophysical profile (BPP), has been the primary means of assessing fetal health in the United States for decades. NST can forecast severe fetal jeopardy [23], but false-positive NST rates in excess of 90% have been reported. On the other hand, only high (>8) BPP scores and low (zero) BPP scores were predictive of normal pH and academic babies respectively, while the BPP score of 6 was a poor predictor of abnormal outcome.

Intrapartum fetal heart rate (FHR) monitoring is a standard of care in the United States. FHR has turned to be a poor predictor of neurological outcome, failing substantially to fulfill the major purpose of using any particular technique: the avoidance of neurological sequelac. Frequently, FHR monitoring has led to unnecessary interference with the birth process, and even to harm through increased rate of cesarean sections. Recent trials using pulse oximetry in the human fetus during labor may provide some insight in fetal oxygenation during labor, but the relevance of scalp or face oxygenation to cerebral oxygenation and hemodynamics should be taken with great caution, especially as it has been shown that the circumstances exist where cerebral hypoxia may develop in the presence of appropriate peripheral arterial and venous oxygen saturation.

Optical spectroscopy could be used to monitor and image tissue blood oxygenation and volume by measuring absorption of oxyhemoglobin and deoxyhemoglobin in the near infrared (NIR) wavelength region. Below 700 nm, light is strongly absorbed by hemoglobin. Above 900 nm, it is strongly absorbed by water. By making differential measurements at either side of the isosbestic point of oxy-hemoglobin and deoxy-hemoglobin absorbance (near 800 nm), it is possible to quantify the blood oxygenation and volume levels. Typically, these measurements are made at 750 nm and 830 nm.

Optical spectroscopy has been used to monitor an intra-partum fetus. Delpy et al. have demonstrated the possibility of intrapartum optical monitoring in human fetuses by using a continuous wave (CW) optical instrument (Hamamatsu NIRO-500 Monitor) and soft rubber probes placed through the cervix of the laboring woman and up against the fetal head to carry

small fiber optic cables transmitting and receiving NIR light (Peebles, D.M. et al., "Changes in human fetal cerebral hemoglobin concentration and oxygenation during labor measured by near-infrared spectroscopy", Am. J. Obstet. Gynecol, 1992; 166:1369-73). They have reported changes in fetal cerebral oxygenation (cerebral desaturation) following variable, late, and prolonged decelerations, (Aldrich, C.J. et al., "Late fetal heart rate decelerations and changes in cerebral oxygenation during the first stage of labour", Br. J. Obstet. Gynaecol. 1995a; 102:9-13); (Aldrich, C.J. et al., "Fetal heart rate changes and cerebral oxygenation measured by near infrared spectroscopy during the first stage of labour", E. J. Obstet. Gynecol. Reprod. Biol., 1996; 64:189-195) as well as with short contraction intervals (Peebles, D.M. et al., "Relation between frequency of uterine contractions and human fetal cerebral oxygen saturation studied during labour by near-infrared spectroscopy", Br. J. Obstet. Gynaecol., 1994; 101:44-48). A significant correlation between cerebral oxygen saturation measured by optical spectroscopy shortly before delivery and fetal umbilical blood gas and acid-base status at birth has been reported, (Aldrich, C.J. et al., "Fetal cerebral oxygenation measured by near-infrared spectroscopy shortly before birth and acid-base status at birth", Obstet. Gynecol., 1994a; 84:861-6) as well as a significant rise in fetal cerebral oxygenation after maternal oxygen administration during normal labor (Aldrich, C.J. et al., "The effect of maternal oxygen administration on human fetal cerebral oxygenation measured during labour by near infrared spectroscopy", Br. J. Obstet. Gynaecol, 1994b; 101:509-513). Changes in maternal posture during labor, in women with effective epidural analgesia, were reportedly associated with a significant decrease in fetal cerebral oxygenation (Aldrich, C.J. et al., "The effect of maternal posture on fetal cerebral oxygenation measured during labour by near infrared spectroscopy", Br. J. Obstet. Gynaecol., 1995b; 102:14-19). Paul Mannheimer (Mannheimer, P.D. et al., "Physio-optical considerations in the design of fetal pulse oximetry sensors", Euro. J. Obstet. & Gyn., 1997; S9-S19) (Reference Notem: "Nellcor Puritan Bennett N-400 fetal oxygen saturation monitoring system: technical issues", Nellcor Puritan Bennett, Inc., Perinatal Note Number 1, Pleasanton, CA 94588) and Swedlow (Swedlow, D.B., Reference Notem: "Nellcor Puritan Bennett N-400 review of evidence for a fetal SpO2 critical threshold of 30%", Nellcor Puritan Bennett, Inc., Perinatal Note Number 2, Pleasanton, CA 94588) have recently published design considerations and recommended limiting arterial desaturation values (30%) for the fetal brain.

There is still a need for a non-invasive, relatively inexpensive technique that can detect, image and characterize a tumor. Furthermore, there is still a need for a non-invasive, relatively

inexpensive technique that can examine and monitor an in utero fetus.

Summary

The present invention relates to various apparatuses and methods for non-invasive optical examination, imaging and monitoring of internal tissue using visible or infra-red light. The invention also relates to non-invasive optical examination, imaging and monitoring of an in utero fetus or fetal tissue.

According to one aspect, the optical examination technique employs an optical system for *in vivo*, non-invasive examination of biological tissue of a subject. The optical system includes an optical module, a controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue. Each optical input port is constructed to introduce visible or infrared light emitted from a light source. Each optical detection port is constructed to receive photons of light that have migrated in the examined tissue region from at least one of the input ports and provide the received light to a light detector. The controller is constructed and arranged to control operation of the light source and the light detector to detect light that has migrated over at least one of the photon migration paths. The processor is connected to receive signals from the detector and arranged to form at least two data sets, a first of the data sets representing blood volume in the examined tissue region and a second of the data sets representing blood oxygenation in the examined tissue region. The processor is arranged to correlate the first and second data sets to detect abnormal tissue in the examined tissue region.

Preferably, the second data set includes hemoglobin deoxygenation values. The processor may be arranged to form a third data set being collected by irradiating a reference tissue region.

According to another aspect, the optical examination technique employs an optical system for *in vivo*, non-invasive examination of biological tissue of a subject. The optical system includes an optical module, a controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue. Each optical input port is constructed to introduce visible or infrared light emitted from a light source. Each optical detection port is constructed to receive photons of light that have migrated in the tissue from at least one of the input ports and provide the received light to a light detector. The controller is constructed and arranged to control operation of the light source and

the light detector to detect light that has migrated over at least one of the photon migration paths. The processor is connected to receive signals from the detector and arranged to form at least two data sets, a first of the data sets being collected by irradiating an examined tissue region of interest and a second of the data sets being collected by irradiating a reference tissue region having similar light scattering and absorptive properties as the examined tissue region. The processor is arranged to correlate the first and second data sets to detect abnormal tissue in the examined tissue region.

According to another aspect, the optical examination technique employs an optical system for *in vivo*, non-invasive examination of biological tissue of a subject. The optical system includes an optical module, a controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue or a model representing biological tissue. Each optical input port is constructed to introduce visible or infrared light emitted from a light source. Each the optical detection port is constructed to receive photons of light that have migrated in the tissue or the model from at least one of the input ports and provide the received light to a light detector. The controller is constructed and arranged to control operation of the light source and the light detector to detect light that has migrated over at least one of the photon migration paths. The processor is connected to receive signals from the detector and arranged to form at least two data sets of two tissue regions, a first of the data sets being collected by irradiating an examined tissue region and a second of the data sets being collected by irradiating a region of a tissue model having selected light scattering and absorptive properties. The processor is arranged to correlate the first and second data sets to detect abnormal tissue in the examined tissue region.

Preferred embodiments of these aspects include one or more of the following features.

The processor may be arranged to correlate the first and second data sets by determining congruence between data of the two data sets.

The processor may be programmed to order the first and second data sets as two-dimensional images and to determine the congruence using the two-dimensional images.

The processor may be programmed to order the first and second data sets as two-dimensional images and to determine the congruence using the following formula:

$$1 - \left(\frac{maximum\ overlap\ residual}{maximum\ selected\ tissue\ signal} \right) \times 100$$

The processor may be further arranged to determine a location of the abnormal tissue within the examined tissue region.

The processor may be adapted to produce from the data set an image data set by implementing an optical tomography algorithm. The optical tomography algorithm may use factors related to determined probability distribution of photons attributable to the scattering character of the tissue being imaged.

The controller may be arranged to activate the source and the detector to obtain a first selected distance between the input and detection ports, and the processor may be arranged to form the data set for the first distance. The processor may produce an image data set from the data set formed for the first distance. The controller may further be arranged to activate the source and the detector to obtain a second selected distance between the input and detection ports and is arranged to form another data set for the second distance.

The optical system may further include a display device constructed to receive the image data set from the processor and to display an image.

The optical system may further include a first oscillator and a phase detector. The first oscillator is constructed to generate a first carrier waveform at a first frequency on the order of 10^8Hz, the first frequency having a time characteristic compatible with the time delay of photon migration from the input port to the detection port. The light source is coupled to the first oscillator and constructed to generate the light modulated by the first carrier waveform. The phase detector is constructed to determine change in waveform of the detected light relative to the waveform of the introduced light and measure therefrom the phase shift of the detected light at the wavelength, wherein the phase-shifted light is indicative of scattering or absorptive properties of the examined tissue region. The processor is arranged to form the data set based on the measured phase shift. This optical system may further include a second oscillator constructed to generate a second waveform at a second frequency. The detector is then arranged to receive a reference waveform at a reference frequency offset by a frequency on the order of 10^3Hz from the first frequency and to produce a signal, at the offset frequency, corresponding to the detected radiation. The phase detector is adapted to compare, at the offset frequency, the detected radiation with the introduced radiation and to determine therefrom the phase shift.

The optical system may further include an oscillator, a phase splitter, and first and second double balanced mixers. The oscillator is constructed to generate a first carrier waveform of a selected frequency compatible with time delay of photon migration from the input port to the

detection port The light source is connected to receive from the oscillator the carrier waveform and is constructed to generate optical radiation modulated at the frequency. The phase splitter is connected to receive the carrier waveform from the oscillator and produce first and second reference phase signals of predefined substantially different phases. The first and second double balanced mixers are connected to receive from the phase splitter the first and second reference phase signals, respectively, and are connected to receive from the detector the detector signal and to produce therefrom a in-phase output signal and a quadrature output signal, respectively. The processor being connected to the double balanced mixers and arranged to receive the in-phase output signal and the quadrature output signal and form therefrom the data set.

The processor may be arranged to calculate a phase shift (Θ_λ) between the light introduced at the input port and the light detected at the detection port prior to forming the data set.

The processor may arranged to calculate an average migration pathlength of photons scattered in the examined tissue between the optical input port and the optical detection port prior to forming the data set.

The processor may further employ the pathlength in quantifying hemoglobin saturation (Y) of the examined tissue.

The processor may be arranged to calculate a signal amplitude (A_λ) determined as a square root of a sum of squares of the in-phase output signal and the quadrature output signal prior to forming the data set.

The optical system may further include a narrow band detector connected to receive from the optical detector the detector signal and to produce a DC output signal therefrom. The processor then further determines a modulation index (M_λ) as a ratio of values of the signal amplitude and the signal amplitude plus the DC output signal.

The optical system may further include at least one oscillator connected to at least one light source. The oscillator is constructed to generate a carrier waveform of a selected frequency. The light source generate slight of a visible or infrared wavelength being intensity modulated at the frequency to achieve a known light pattern. The controller is constructed to control the emitted light intensity or phase relationship of patterns simultaneously introduced from multiple input ports, wherein the introduced patterns form resulting radiation that possesses a substantial gradient of photon density in at least one direction. This resulting radiation is scattered and absorbed over the migration paths. The detector is constructed and arranged to detect over time

8

the resulting radiation that has migrated in the tissue to the detection port. The processor is further arranged to process signals of the detected resulting radiation in relation to the introduced radiation to create the data sets indicative of influence of the examined tissue upon the substantial gradient of photon density of the resulting radiation.

The optical system may further include a phase detector constructed to detect the phase of the detected radiation and provide the phase to the processor.

The optical system may further include an amplitude detector constructed to detect the amplitude of the detected radiation and provide the amplitude to the processor.

The phase relationship of light patterns introduced from two input ports may be 180 degrees.

The optical system may be constructed as described in U.S. Patent 5,119,815 or 5, 386,827. This system includes a light source constructed to generate pulses of radiation of the wavelength, the pulses having a known pulse wave form of a duration on the order of a nanosecond or less. An optical detector is constructed to detect over time photons of modified pulses that have migrated in the tissue from the input ports. This system also includes an analyzer connected to the detector and adapted to determine a change in the pulse waveform shape of the detected pulses relative to the introduced pulses, at the employed wavelength. The processor then creates the data set based on the determined pulse waveform change. The processor may also be constructed and arranged to calculate the effective pathlength of photons of the wavelength migrating between the input and detection ports in conjunction with creating the data set. The processor may also be constructed and arranged to calculate the scattering coefficient at the wavelength in conjunction with creating the image data set The processor may also be constructed and arranged to calculate the absorption coefficient at the wavelength in conjunction with creating the data set.

The optical system may use the light source that produces relatively long light pulses and the processor that forms the data set by subtracting amplitude of two the pulses emitted from two input ports located symmetrically relative to one detection port.

The optical system may be constructed to introduce and detect photons at two wavelengths selected to be sensitive to a tissue constituent. The tissue constituent may be an endogenous pigment or an exogenous pigment. The endogenous pigment may be hemoglobin. The exogenous pigment may be a selected contrast agent.

According to another aspect, an optical apparatus for *in vivo*, non-invasive,

transabdominal examination of fetal tissue includes an optical module, a controller, and a processor. The optical module includes an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside the uterus. Each optical input port is constructed to introduce visible or infrared light

5   emitted from a light source. Each optical detection port is constructed to receive photons of light that have migrated from at least one of the input ports and provide the received light to a light detector. The controller constructed and arranged to control operation of the light source and the light detector to detect photons that have migrated over at least one of the photon migration paths inside fetal tissue. The processor connected to receive signals from the detector and arranged to

10   characterize the fetal tissue region.

Preferred embodiments of this aspect include have one or more of the following features.

The controller and the processor may be arranged to evaluate the optical data and subsequently control operation of the light source and the light detector to collect additional optical data corresponding to photons that have partially migrated inside brain tissue of the fetus.

15   The optical module may be constructed for placement on the abdomen based on locating the head of the fetus by an ultrasound system so that the optical data correspond to photons that have partially migrated inside brain tissue of the fetus.

The processor may be arranged to determine hemoglobin oxygenation of the fetal tissue or a pulse rate of the fetus. The processor may be arranged to create an image the brain tissue.

20   The processor may be arranged to create images blood volume in the brain tissue and blood oxygenation in the brain tissue.

According to another aspect, an optical method for *in vivo*, non-invasive, transabdominal examination of fetal tissue is provided. The method includes placing the optical module on the exterior of the abdomen of the pregnant female subject; introducing visible or infrared light from

25   at least one the optical input port into the uterus and receiving photons that have migrated in the uterus to at least one of the detection ports; detecting the received photons by at least one optical detector optically coupled to the least one detection port; controlling the introducing and detecting steps to collect optical data corresponding to photons of light that have partially migrated inside a fetal tissue region; and processing the optical data to characterize the fetal

30   tissue region.

According to another aspect, the described optical techniques can be used to examine, monitor or image selected tissue of an in utero fetus. To collect the optical data, the techniques

can employ different optical modules designed for targeting *in vivo*, non-invasively the fetus. The optical module includes an array of optical input ports and optical detection ports located over selected geometrical patterns that provide a multiplicity of photon migration paths. The photon migration paths partially include the selected fetal tissue such as the fetus's brain. The

5   optical module may be moved around the exterior of the abdomen to locate the selected tissue of the fetus (e.g., the head) within the photon migration paths. The optical apparatus can provide single wavelength or multiple wavelength data of the fetal tissue, wherein an employed wavelength is sensitive to absorption or scattering by a tissue constituent (e.g., hemoglobin, or an introduced contrast agent). The optical apparatus may also generate blood volume, hemoglobin

10   oxygenation or hemoglobin deoxygenation data, or data sensitive to any other tissue constituent. Based on the optical data, the apparatus may also measure the heart rate of the fetus, for example, by techniques used in pulse oximetry.

The optical imaging apparatus can further generate blood volume, hemoglobin oxygenation or hemoglobin deoxygenation images, or images of any other tissue constituent

15   based on single or multiple wavelength optical data. The apparatus can use different images processing and enhancing algorithms known in the art. The apparatus can be used for a short term or prolonged transabdominal monitoring or for routine examination of the fetus. The apparatus may also be used for monitoring while in labor, wherein a clinician makes a decision about the state of the fetus based on the optical data.

20   The optical system can also include a stimulator constructed to stimulate a selected functional activity of the examined fetal tissue. The stimulator is constructed to deliver electrical signals, electromagnetic signals, vibroaccoustic signals, or sound such as loud rhythmic music to the fetus. Alternatively, the stimulator can deliver chemical substances to the fetus. For example, oxytocin may be administered intravenously to the pregnant female to induce uterine

25   contractions. The pregnant female can ingest cold liquids or carbohydrates (fructose, glucose, complex carbohydrates), or can change her body position creating changes in uterine pressure to stimulate the fetus. The optical system can collect data before, during and after the simulation.

The described optical techniques can also be used in combination with ultrasound techniques, X-ray techniques (including CT), or magnetic resonance imaging (MRI or *f*MRI).

30   These techniques may be used acquire data that are correlated with the optical data. To collect the optical data, the optical apparatus may employ different optical modules suitable for targeting the fetus at a different developmental stage. The optical modules include an array of light

sources and light detectors located in a selected geometrical patterns to provide a multiplicity of source-detector paths of photon migration inside the examined fetal organ. For example, the ultrasound technique is used to locate the fetal heart and then the described optical technique can non-invasively characterize the blood volume and oxygenation.

The described optical imaging systems may generate single wavelength or multiple wavelength images of the examined tissue, wherein the used wavelength is sensitive to absorption or scattering by a tissue constituent (e.g., an endogenous or exogenous pigment, tissue cells) or is sensitive to structural changes in the tissue. The optical images may display tissue absorption, tissue scattering or both. The optical imaging systems may also generate blood volume and hemoglobin deoxygenation images of the examined organ, or may generate images of any other tissue constituent based on multiple wavelength optical data. A processor may employ different image processing and enhancing algorithms known in the art.

The optical imaging system may collect single wavelength or multiple wavelength data of a tissue model for calibration, or for detection of background data. In the calibration procedure, the optical module is placed on the model and the imaging system collects a limited number of optical data or collects optical data using the same sequences as used during the tissue examination. The system may either store the model data for a subsequent digital processing, or may adjust the source or detector gains to detect optical data according to a selected pattern. The imaging system may use different organ models having the same scattering coefficient or the same absorption coefficient as the normal tissue of the organ. The model may also include a representation of the abdominal wall (or a representation of other "obscuring" tissue structures, such as blood vessels, organs, or ribs) having the same scattering coefficient and the same absorption coefficient as the abdominal wall. The model tissue may have the scattering and absorption coefficient of abnormal or infected tissue approximating an examined organ. Furthermore, the models may have different sizes and shapes.

In general, an optical examination technique employs an optical system for *in vivo* non-invasive imaging of a region of biological tissue of a subject. The optical imaging system includes an optical module, a controller and a processor. The optical module includes an array of optical input ports and optical detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside the biological tissue of interest. Each optical input port is constructed to introduce into the tissue volume visible or infrared light emitted from a light source. Each optical detection port is constructed to provide light from the tissue to a

light detector. The controller is constructed and arranged to activate one or several light sources and light detectors so that the light detector detects light that has migrated over at least one of the photon migration paths. The processor receives signals corresponding to the detected light and creates at least one data set representing the examined tissue. The processor may also produce a spatial image of the examined tissue region.

To characterize the examined tissue, the imaging system can correlate several images of blood volume, hemoglobin oxygenation, hemoglobin deoxygenation, or images sensitive to an optical contrast agent. The imaging system can correlate images of the same tissue region taken at different times. The imaging system can correlate images of "symmetric" tissue, such as tissue of different region of the same organ (e.g., the liver, the lungs) or symmetric organs (e.g., the right and left kidney, the right and left brain hemisphere, the right and left leg, the right and left arm). The imaging system can correlate images of tissue with images of a tissue model. The correlation of the images identifies pathological tissue regions, such as tumors undergoing angiogenetic growth or hypermetabolism, wherein the tumor area exhibits an increased blood volume and decreased hemoglobin oxygenation. Furthermore, the correlation of the images can be used to monitor inhibition of angiogenesis during or after drug treatment.

To collect the optical data, the described optical examination techniques can use one or several optical modules having different design. The optical modules are constructed to target a selected tissue region of the examined organs by specific geometrical patterns of source-detector photon migration paths. Each source is displaced from one or several detectors by a spacing between about 1 cm and 25 cm (preferably 4 cm and 15 cm and more preferably 10 cm) to establish a "banana-shaped" or a "cigar-shaped" probability gradient of migrating photons in the tissue. Alternatively, each detector is displaced from one or several sources by a spacing between about 1 cm and 25 cm (preferably 4 cm and 15 cm, and more preferably 10 cm) to establish a "banana-shaped" or a "cigar-shaped" probability gradient of migrating photons. By changing the spacings, the optical module can target tissue at different depths and thus obtain three-dimensional optical data. Preferably, the optical module includes a plurality of symmetrical pairs of photon migration paths.

The described techniques can generate the amplitude cancellation or phase cancellation optical patterns, which demonstrate for single or multiple source-detector pairs remarkable sensitivity to small objects. Using back-projection algorithms or other imaging algorithms, it is possible to image a tissue region in less than a minute and with two dimensional resolutions of

<1 cm in two dimensional displays. The present optical techniques can be used to examine internal tissue of an adult, child, neonate or in utero fetus and evaluate tissue functionality, physiology or pathological abnormality.

The present invention also features apparatuses and methods of producing an image from a volume of biological tissue of a living subject. The methods include the steps of providing and using on the subject an imaging apparatus according to any of the foregoing aspects. In certain preferred embodiments, an optical contrast agent or a drug is introduced to the blood stream of the subject, and the apparatus is employed to produce image data sets of the examined tissue while the contrast agent or drug is present in blood or the tissue of the subject. The introduced contrast agent or drug may be preferentially absorbed in a localized tissue type or structure.

Other advantages and features of the invention will be apparent from the following description of the preferred embodiment and from the claims.

Brief Description of the Drawings

Figs. 1, 1A and 1B show different optical modules located on the abdomen of a pregnant woman.

Fig. 1C is a cross-sectional view of the uterus of woman shown in Fig. 1 displaying light emitted from the optical modules shown in Fig. 1A or 1B.

Figs. 2, 2A and 2B show different optical modules located on the back of a subject for transabdominal or transthoracic examination.

Figs. 3 and 3A show diagrammatically respective single wavelength and dual wavelength phase cancellation imaging systems that employ the optical module of Fig. 1A or Fig. 1B.

Fig. 3B is a timing diagram used by the imaging system of Figs. 3 and 3A.

Figs. 4 and 4A show diagrammatically another embodiment of the phase cancellation imaging system employing the optical module of Fig. 1A.

Fig. 5 shows diagrammatically another embodiment of the phase cancellation imaging system employing the optical module of Fig. 1A.

Fig. 6 shows schematically an amplitude cancellation imaging system using another embodiment of the optical module shown in Fig. 6A.

Figs. 7, 7A and 7B show different embodiments of a cooling module used with a broad band light source such as a tungsten light bulb.

Fig. 8 shows diagrammatically another embodiment of the amplitude cancellation

imaging system employing the optical module of Fig. 1B

Fig. 8A shows a circuit configuration for one element of the amplitude cancellation imaging system of Fig. 8.

Fig. 8B is a timing diagram used by the imaging system of Fig. 8.

Fig. 8C shows diagrammatically one channel of the amplitude cancellation imaging system of Fig. 8.

Fig. 8D shows diagrammatically another embodiment of the amplitude cancellation imaging system of Fig. 8.

Fig. 9 is an example of a "four-dimensional" graph for summarizing optical data and characterizing suspicious tissue structures.

Description of the Preferred Embodiments

Referring to Figs. 1 through 2B, a selected fetal tissue of a fetus inside a female subject 8 is examined non-invasively using an imaging system connected to an optical module 12 or 14. Optical modules 12 and 14 include a multiplicity of light sources (e.g., laser diodes, LEDs, flashlight bulbs) providing light in the visible to infrared range and light detectors (e.g., photo multiplier tubes, Si diode detector, PIN, avalanche or other diode detectors), which may also include interference filters. The light sources and the light detectors are arranged to form selected geometrical patterns that provide a multiplicity of source-detector paths of photon migration inside the examined organ. The imaging system provides an *in vivo* image of the examined tissue. The image shows a location and size of an abnormal structure in the tissue, such as a tumor or bleeding. Furthermore, the image provides a qualitative and quantitative measure (e.g., metabolism, metabolic biochemistry, pathophysiology) of the abnormal structure. Alternatively, an optical module includes a multiplicity of optical fibers connected to one or several light sources, and a multiplicity of optical detection fibers connected to one or several light detectors as described in the PCT applications PCT/US96/00235 and PCT/US96/11630 (filed January 2, 1996 and July 12, 1996), both of which are incorporated by reference.

In one embodiment, optical module 12 includes nine laser diodes S_1, S_2,..., S_9 and four photo multiplier tubes (PMTs) D_1, D_2, D_3, D_4. The laser diodes and PMTs are embedded in a pliable rubber-like material positioned in contact with the scalp. There is a Saran (R) wrap or similar material located between the laser diodes and the skin, and between the PMTs and the skin. Similarly, optical module 14 includes four laser diodes S_1, S_2, S_3, S_4 and 27 silicon diode

detectors D_1, D_2, ..., D_{27} embedded in a pliable rubber-like material. The imaging systems shown in Figs. 3 through 7 may be interfaced with optical module 12 or 14 for imaging of the tissue. Furthermore, the imaging systems shown in Figs. 3 through 7, may be interfaced with two identical optical modules (12 or 14) located to probe symmetrical organs or tissue regions, such as the right kidney and the left kidney for lateralization, that is, comparative examination of the symmetric parts of the tissue. For calibration, the optical module may also be placed on one or several models having the same scattering coefficient and the same absorption coefficient as the normal tissue of the examined organ.

Referring to Figs. 1A and 3, a phased array imaging system 15 is connected to optical module 12 with nine laser diodes S_1, S_2,..., S_9 and four PMTs D_1, D_2, D_3, D_4 (e.g., Hamamatsu R928, Hamamatsu R1645u, TO8 1 cm^2 GaAs photomultiplier tube) powered by a high voltage supply (not shown). Four laser diodes surround each PMT forming an equidistant arrangement (for example, different optical modules may use distances of 3.5 cm, 7 cm, 10 cm, or 15 cm). A switch 18 connects laser diodes S_1, S_2,..., S_9 to a phase splitter 20, which provides to the diodes an RF modulation signal having both a 0 degree phase and a 180 degree phase. Imaging system 15 also includes a 50 MHz single side band transmitter 22 connected by a phase lock loop 24 to a 50 MHz single side band receiver 26. Single side band (SSB) transmitter 22 is connected to a 1kHz oscillator 28, which provides a reference signal 30 to a phase detector 32. SSB receiver 26 is connected to a switch 27, which connects one of the four PMTs (0.5 µV sensitivity) depending on control signals from a controller 19. The SSB transmitter-receiver pair can operate in the frequency region of 10-1000 MHz (preferably 50-450 MHz). The SSB receiver detects signal levels on the order of microvolts in a 2 KHz bandwidth. The phase noise of this apparatus is less than about 0.1°. This narrow bandwidth limits the spread of switching of various light sources to approximately 1.0 msec, and thus the sequencing time for an entire image of 16 source detector combinations can be ~1 sec. The system uses a 1 sec averaging time.

Controller 19, connected to a personal computer (not shown), sequences laser diodes S_1, S_2,..., S_9 so that two diodes receive 0° phase and 180° phase signals from splitter 20, every 0.1 sec. At the same time, controller 19 connects a symmetrically located PMT to SSB receiver 26. As shown in a timing diagram 40 (Fig. 3B), phased array imaging system 15 triggers two sources so that they emit modulated light of a 0° phase and a 180° phase for about 100 msec, and at the same time triggers a symmetrically located PMT. For example, when laser diodes 1 (S_1) and 2 (S_2) emit light of a 0° and 180° phase, respectively, and detector 1 (D_1) detects light that has

migrated in the examined tissue. SSB receiver 26, which is phase locked with SSB transmitter 22, receives signal from detector 1 and provides output signal 34 to phase detector 32. Phase detector 32 measures the phase (36) of the detected light, and SSB receiver 26 provides the amplitude (38) of the detected light. This phase detection circuit was described in U.S. Patent 4,972,331, which is incorporated by reference.

In the next cycle, controller 19 directs switch 18 to connect laser diodes 2 (S_2) and 3 (S_3), which emit modulated light of a 0° phase and a 180° phase, respectively, and detector 2 (D_2) detects light that has migrated in the examined tissue. Controller 19 also directs switch 27 to connect detector 2 to SSB receiver 26, which receives detection signal corresponding to the photons that have migrated from laser diodes 2 and 3 to detector 2. Again, phase detector 32 measures the phase (36) of the detected light, and SSB receiver 26 provides the amplitude (38) of the detected light. The duration of each pair of light flashes is 100 msec. The complete set of data for all source - detector combinations is collected every 30 sec. A computer (not shown) stores the phase values and the amplitude values measured for the different combinations shown in timing diagram 40 and employs these values to create images of the examined tissue, as is described below. The computer uses the ADA2210 board for data acquisition.

Before or after the above-described measurement, phased array imaging system 15 may be calibrated on a model of the uterus and the fetus. The in utero fetal model includes a large vessel that models the uterus and a smaller chamber that models the fetal head. This chamber can be placed several centimeters deep as is the fetal head beneath the abdominal and uterine layers. The fetal head chamber is filled with Intralipid® (scatterer) and human blood (absorber), and the large vessel with amniotic fluid (water). The model is constructed to change in blood oxygenation and blood volume using a tubing connected to the chamber. The calibration includes a variety of fetal conditions over a range of blood oxygenation and volume values of the fetal brain as well as a range of optical properties and thickness of the uterine and abdominal tissue layers.

During the calibration procedure, the optical module is placed on the model. and the imaging system collects the phase data and the amplitude data using the sequences shown in the timing diagram 40. The scattering coefficient and the absorption coefficient of different types of tissue can be measured as described in U.S. Patent 5,402,778, which is incorporated by reference. Furthermore, the optical signals are measured as a function of change in the position of the fetal head to determine the signal displacement as a function of fetal head position. The

sensitivity and detection limit is a function of the blood oxygenation and volume of the fetal brain, the maternal tissues and the various positions of the fetal head with respect to the source and detector for both the short and long source-detector separations (i.e., the relative volume of the fetal tissue and amniotic fluid). The phased array system has a very high positional accuracy and object detection at a depth of several centimeters inside the model.

Phased array imaging system 15 generates a "model" image for each wavelength employed. The model image may later be subtracted from the tissue images to calibrate the system and also account for the boundary conditions of the light migrating in the tissue. Alternatively, phased array imaging system 15 is calibrated prior to taking measurement data and the gain on the light sources or the detectors is adjusted to obtain selected values.

Referring to Figs. 1A and 3A, a dual wavelength phased array imaging system 45 is connected to optical module 12 with nine 780 nm laser diodes S_1, S_2,..., S_9, nine 830 nm laser diodes S_{1a}, S_{2a},..., S_{9a}, and the four PMTs D_1, D_2, D_3, and D_4 powered by a high voltage supply (not shown). Pairs of laser diodes S_1 and S_{1a}, S_2 and S_{2a}, ..., S_9 and S_{9a} are located next to each other and arranged to introduce modulated light at almost the same tissue locations. A switch 48 connects laser diodes S_1, S_2,..., S_9 to a phase splitter 50, which provides to the laser diodes an RF modulation signal having both a 0 degree phase and a 180 degree phase. Similarly, a switch 48a connects laser diodes S_{1a}, S_{2a},..., S_{9a} to a phase splitter 50a, which provides to the laser diodes an RF modulation signal having both a 0 degree phase and a 180 degree phase. A 52 MHz SSB transmitter 52 is connected by a phase lock loop 54 to a 52 MHz SSB receiver 56, and a 50 MHz SSB transmitter 52a is connected by a phase lock loop 54a to a 50 MHz SSB receiver 56a. Both SSB transmitters 52 and 52a are connected to a 1kHz oscillator 58, which provides a reference signal 60 to phase detectors 62 and 62a. SSB receivers 56 and 56a are connected one of the four PMTs by a switch 57 depending on control signals from controller 49. Controller 49, connected to a personal computer, sequences the laser diodes so that two pairs of the laser diodes receive 0° phase and 180° phase signals from splitters 50 and 50a, and at the same time controller 49 connects a symmetrically located detector to SSB receivers 56 and 56a.

As shown in timing diagram 40 (Fig. 3B), phased array imaging system 45 triggers for each wavelength two sources that emit simultaneously modulated light of a 0° phase and a 180° phase for about 100 msec and, at the same time, controller 49 connects the symmetrically located PMT. For example, switch 48 connects SSB transmitter 52 to 780 nm laser diode 4 (S_4) to emit 52 MHz modulated light of a 180° phase and connects 780 nm laser diode 5 (S_5) to emit 52 MHz

modulated light of a 0° phase. At the same time, switch 48a connects SSB transmitter 52a to 830⁻ nm laser diode 4a (S_{4a}) to emit 50 MHz modulated light of a 180° phase and connects 830 nm laser diode 5a (S_{5a}) to emit 52 MHz modulated light of a 0° phase. Simultaneously, switch 57 connects detector 1 (D_1) to SSB receivers 56 and 56a to receive the detection signal

5   corresponding to photons of both wavelengths that have migrated in the examined tissue. Phase detector 62 provides the phase (66) of the detected 780 nm light, and phase detector 62a provides the phase (66a) of the detected 830 nm light for the selected geometry. Similarly, SSB receiver 56 measures the amplitude (68) of the detected 780 nm light and SSB receiver 56a measures the amplitude (68a) of the detected 830 nm light. This operation is repeated for all combinations of

10   sources and detectors shown in timing diagram 40. A computer (not shown) stores the phase value and the amplitude value measured for the different combinations shown in timing diagram 40. The computer then uses the measured values to create images using appropriate algorithms.

Several phased array systems were described in the PCT application PCT/US 93/05868 (published as WO 93/2514 on December 23, 1993), which is incorporated by reference. This

15   PCT publication also describes the basic principles of phase and amplitude cancellation. The phased array imaging system uses a detector for detecting light emitted from equidistant sources located symmetrically with respect to the detector (or one source and several equidistant detectors located symmetrically). If two sources S_1 and S_2 emit modulated light having equal amplitude and a 0° phase and a 180° phase, detector D_1 located in the middle detects a null in the

20   amplitude signal and detects a crossover between the 0° and 180° phase, i.e., a 90° phase, for substantially homogeneous tissue. That is, the detector is located on the null plane. In heterogeneous tissue, the null plane is displaced from the geometric midline. Nevertheless, the null establishes an extremely sensitive measure to perturbation by an absorber or scatterer. Furthermore, at the null condition, the system is relatively insensitive to amplitude fluctuations

25   common to both light sources, and insensitive to inhomogeneities that affect a large tissue. The system has a high sensitivity to scattering provided that the scattering contrast is the same as the absorbing contrast. The system can readily observe shifts of 50 to 60° of phase under altered blood volume or blood oxygenation conditions, where the phase noise is less than a 0.1° (s/n >400) for a 1 Hz bandwidth. The amplitude signal is little less useful in imaging since the

30   position indication is somewhat ambiguous, i.e., an increase of signal is observed regardless of the displacement of the absorbing object with respect to the null plane, although this is remedied by further encoding of the sources.

As described in the PCT application PCT/US 93/05868, the light sources excite a photon diffusion wave, due to cancellation effects, that has a relatively long wavelength (~10 cm), determined by the scattering ($\mu_s' = 10$ cm^{-1}) and absorption ($\mu_a = 0.04$ cm^{-1}) properties of the tissue. The photon diffusion wavelength of about 10 cm provides imaging in the "near field." The imaging system may use light sources of one or several optical wavelengths in the visible to infrared range, depending on the characteristic to be imaged (i.e., blood volume, blood oxygenation, a distribution of a contrast agent in the tissue, an absorbing constituent of the tissue, a fluorescing constituent of the tissue, or other). The phase signal at zero crossing detection is essentially a square wave "overloaded" signal. It is moderately insensitive to the changes of signal amplitude that may occur in imaging from proximal to distal source-detector pairs and is also moderately insensitive to ambient light.

Referring to Fig. 4, in another embodiment, a phased array imaging system 100 is used instead of imaging systems 15 or 45. Imaging system 100, connected to optical module 12 (shown in Fig. 1A) having nine laser diodes S_1, S_2,..., S_9 and four PMTs D_1, D_2, D_3, and D_4, employs homodyne phase detection. A switch 102 connects laser diodes S_1, S_2,..., S_9 to a phase splitter 104, which provides to the diodes an RF modulation signal having both a 0 degree phase and a 180 degree phase. Imaging system 100 also includes a 200 MHz oscillator 106 providing RF signal to a driver 108, which is connected to phase splitter 104. (Alternatively, an oscillator in the range of 10 - 1000 MHz, preferably 50 - 500 MHz, may be used.) A phase shifter 114 receives the drive signal (112) from driver 108 and provides the signal of a selected phase (e.g., a 0° phase change) to a 90° phase splitter 116. Phase splitter 116 provides a 0° phase signal (118) and a 90° phase signal (120) to double balance mixers (DBM) 122 and 124, respectively.

A controller 140, connected to a personal computer (PC), sequences laser diodes S_1, S_2,..., S_9 using switch 102 so that two diodes receive modulate signal at a 0° phase and a 180° phase from splitter 104. At the same time, a controller 140 connects a symmetrically located PMT using a switch 130 to an amplifier 134. Amplifier 134 provides a detection signal (136) to double balance mixers 122 and 124, and to a DC detector 138. Double balance mixer 122 receives the detection signal (136) and the 0° phase reference signal (118) and provides an in-phase signal I (144). Double balance mixer 124 receives the detection signal (136) and the 90° phase reference signal (120) and provides a quadrature signal R (142). DC detector 138 provides DC signal (146). The in-phase signal I and quadrature signal R specify the phase ($\theta = \tan^{-1}I/R$) of the detected optical radiation and the amplitude ($A = (R^2 + I^2)^{-\frac{1}{2}}$) of the detected optical

radiation. This phase detection circuit was described in U.S. Patent 5,553,614, which is incorporated by reference.

Similarly as for imaging systems 15 and 45, imaging system 100 directs controller 140 to sequence the laser diodes and the PMT detectors using timing diagram 40. The computer stores

5   the phase value and the amplitude value measured for each of the combinations and generates images described below.

Fig. 4A shows diagrammatically one portion of phase cancellation, phased array imaging system 100. The depicted portion of imaging system 100 includes two laser diodes LD_1, and LD_2 and a light detector D_1, which are included in optical module 12 or 14. Oscillator 106

10   provides carrier waveform having a frequency in range of 30 to 140 MHz. The carrier waveform frequency is selected depending on the operation of the system. When time multiplexing the light sources using switch 102, then the carrier waveform is modulated at a lower frequency, e.g., 30 MHz to afford switching time.

When no time multiplexing is performed, oscillator 106 operates in the 100 MHz region.

15   Splitter 104 splits the oscillator waveform into 0° and 180° signals that are then attenuated by digitally controlled attenuators 107A and 107B by 0% to 10% in amplitude. The phase of the attenuated signals is appropriately shifted by digitally controlled phase shifters 109A and 109B in the range of 10° - 30°· and preferably 20° in phase. Laser drivers 108A and 108B drive LD_1 and LD_2, respectively, which emit light of the same wavelength, for example, 780 or 800 nm.

20   After the introduced light migrates in the examined tissued, a PMT detector D_1 amplifies the detected signals having initially the 0 and 180° phases. As described above, for homogeneous tissue and symmetric locations of LD_1, LD_2 and D_1, the output of the PMT is 90°, i.e., halfway between 0° and 180° and the amplitude is close to zero. The personal computer (PC) adjusts the attenuation provided by attenuator 107B and the phase shift provided by phase shifter 109B so

25   that detector D_1 detects phase nominally around 25° and amplitude nominally around ≤ 10 millivolts for homogeneous tissue. This signal is connected to amplifier 134 and to the IQ circuit 139. The cosine and sine signals are fed into the personal computer, which takes the amplitude (the square root of the sum of the squares of I and Q) and the phase angle (the angle whose tangent is I/Q) to give outputs of phase around 25° and amplitude signals around 10 millivolts.

30   The personal computer also adjusts the reference signal to the IQ to have the phase ϕ_3 between 10° to 30° and preferably around 25°, i.e., phase shifter 114 provides to the IQ circuit 139 the reference phase having a value selected by the combination of phase shifters 109A and 109B.

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In a currently preferred embodiment, splitter 104 is a two way 180° power splitter model number ZSCJ-2 1, available from Mini-Circuits (P.O. Box 350186, Brooklyn, New York 11235-0003). The phase shifters 109A, 109B and 114 and attenuators 107A, and 107B are also available from Mini-Circuits, wherein the attenuators can be high isolation amplifier MAN-1AD. IQ demodulator 139 is a demodulator MIQY-140D also available from Mini-Circuits.

The system obtains the initial values of attenuator 107B (A_2) and phase shifter 109B (ϕ_2) on a model or a symmetric tissue region (e.g., the contralateral kidney or another region of the same organ that is tumor free). The entire probe is calibrated on a tissue model by storing the calibration values of A_2 and ϕ_2 for the various source-detector combinations (i.e., the baseline image). The probe is then moved to the abdomen, for example, and the phases and amplitudes are detected for the various source and detector combinations. When the contralateral tumor free kidney is used as a model, the probe is transferred to the contralateral kidney (taking note to rotate the probe because of the mirror image nature of the kidney physiology) and then the images are read out from all the source-detector combinations to acquire the tissue image.

There is no limitation on multiplexing as long as the bandwidth of F_1 and F_2 is recognized as being the limiting condition in the system normalization. It should be noted that normalization must be accurate and without "dither" and therefore, a significant amount of filtering in F_1 and F_2, i.e., less than 10 Hz bandwidth. If ϕ_2 is adjusted over a large range, there will be an amplitude-phase crosstalk. Thus, the system may adjust phase and then amplitude and repeat these adjustments iteratively because of the amplitude phase crosstalk. The control of A_1 and ϕ_1 provides even a greater range of control, where obviously inverse signals would be applied to them, i.e., as the $A_1\phi_1$ signals are increased, the A_2, ϕ_2 signals would be decreased. Both A_2 and ϕ_2 can be controlled by PIN diodes, to achieve an extremely wideband frequency range. However, since signal processing controls the bandwidth of the feedback system, that either PIN diode or relay control of the phase and amplitude is feasible for automatic compensation. If, in addition, dual wavelength or triple wavelength sources are used, each one of them must be separately calibrated because no two light sources can be in the same position relative to the imaged tissue (unless, of course, they are combined with optical fibers).

Referring to Fig. 5, in another embodiment, a dual wavelength phased array optical system 150 is used instead of optical systems 15, 45 or 100. Optical system 150, connected to optical module 12 (shown in Fig. 1A) having nine 760 nm laser diodes $S_1, S_2,..., S_9$, nine 840 nm laser diodes $S_{1a}, S_{2a},..., S_{9a}$ and four PMTs $D_1, D_2, D_3,$ and D_4 is based on heterodyne phase

detection. A switch 152 connects the laser diodes to a phase splitter 154, which provides to the diodes an RF modulation signal having both a 0 degree phase and a 180 degree phase. Imaging system 150 employs a mixer 165 connected to a 200 MHz oscillator 160 and 200.025 MHz oscillator 162 (Alternatively, oscillators operating in the range of 10 - 1000 MHz, preferably 50 - 500 MHz, may be used.) Mixer 165 provides a 25 kHz reference signal (168) to an adjustable gain controller 177. Oscillator 162 connected to power amplifier 163 provides a 200.025 MHz reference signal (170) to the second dynode of each PMT detector for heterodyne detection. Each PMT detector provides a 25 kHz detection signal (172) to a switch 178, which in turn provides the signal to a 25 kHz filter 180. A phase detector 184 is connected to an adjustable gain controller 182, which provides a filtered and amplified detection signal (186) and to adjustable gain controller 177, which provides the reference signal (188). Phase detector 184, connected to a switch 190, provides the detected phase value for each wavelength. This phase detection circuit was described in U.S. Patent 5,187,672, which is incorporated by reference. Another type of phase detection circuit was described in U.S. Patent 5,564,417, which is incorporated by reference.

Similarly as described above, controller 175, connected to a personal computer, sequences laser diodes S_1, S_2,..., S_9 or laser diodes S_{1a}, S_{2a},..., S_{9a} using switch 152 so that two diodes emitting the same wavelength receive 0° phase and 180° phase signals from splitter 154. At the same time, controller 175 connects a symmetrically located PMT using a switch 178 to filter 180 and adjustable gain controller 182. Phase detector 184 provides the measured phase. Imaging system employs timing diagram 40 (Fig. 3B); however, since the two wavelength light is not frequency encoded, laser diodes S_1, S_2,..., S_9 or laser diodes S_{1a}, S_{2a},..., S_{9a} are triggered in each sequence. That is, light of only one wavelength is detected in each cycle. For each wavelength, the computer stores the phase values measured for the different combinations. The computer also generates images described below.

Referring to Fig. 6, in another embodiment, an amplitude cancellation imaging system 200 uses an optical module 212 shown in Fig. 6B. Optical module 212 includes twelve light sources S1, S2, ..., S12 and four light detectors D1, D2, D3, and D4 mounted on a plastic or rubber foam material. The light sources and the light detectors are located on a geometrical pattern that provides sixteen source-detector combinations (C1, C2, ..., C16) having a selected source-detector separation. The separation may be 2.5 cm to produce about 1.25 cm average light penetration. (Several modules with different source-detector separations may be used to

obtain several two dimensional images of different tissue depths. Alternatively, a single module may include source detector combinations providing different separations. The light penetration depth is approximately one half of the source-detector separation.) The light sources are 1 W tungsten light bulbs, which emit broad band non-modulated light. The light detectors are silicon

5   diodes, each equipped with an interference filter transmitting a 10 nm wide band centered at 760 nm and 850 nm. The 760 nm and 850 nm wavelengths are selected to detect oxyhemoglobin and deoxyhemoglobin in the examined tissue.

        Optical module 212 is connected to an analog circuit 202, which includes a source circuit 204 for controlling sources S1, S2, ... S12. Optical module 212 is connected to a detector circuit

10   206, which controls diode detectors D1, D2, D3 and D4. In general, imaging system 200 can turn ON each source for a selected period in the range of 10^{-6} sec. to 0.1 sec., and one or several symmetrically located detectors are turned on simultaneously or sequentially to collect optical data. Specifically, one of sources S1, S2, ... S12 is turned ON for 500 msec and the emitted light is introduced into the tissue from the corresponding input port. The introduced photons migrate

15   over banana shaped paths in the examined tissue to a detection port. The corresponding detector is triggered 200 msec. after the source and collects light for 200 msec. Detector circuit 206 receives a detector signal from the diode detector. Detection circuit 206 enables correction for the dark current/noise that comprises background light, DC offset of the operational amplifiers, photodiode dark current, temperature effects on the outputs of individual components and

20   variations due to changing environment.

        Imaging system 200 performs data acquisition in four steps synchronized by its internal oscillator. The first step is performed by having the light sources OFF. The detector output is directed to an integrator 216 and integration capacitor 218 is charged to the dark level voltage. In the second step, the light source is turned ON and after 200 msec the preamplifier output that

25   corresponds to the intensity of the detected light is directed to integrator 216 in a way to charge capacitor 218 with current of polarity opposite to the polarity of the charging current in the first step. This is achieved using an appropriate ON/OFF combination of switches A and B. The voltage of capacitor 218 is charging to a value that, after 200 msec., represents the total detected intensity minus the dark level noise signal. In the third step, both switches A and B are turned

30   OFF to disconnect both the positive unity gain and the negative unity gain operational amplifiers (220 and 222). Then, the output of integrator 218 is moved via switch C to an analog-to-digital converter and the digital signal is stored in the memory of a computer. In the fourth step, the

switches A, B and C are open and switch D is closed in order to discharge capacitor 218 through a 47K resistor. At this point, the circuit of integrator 216 is reset to zero and ready for the first step of the detection cycle.

Alternatively, analog circuit 202 may be replaced by a computer with an analog-to-digital converter and appropriate software that controls the entire operation of optical module 212. The computer controls the sources and the detectors of optical module 212 in a similar way as described above. The detected dark level noise signal is digitally subtracted from the detected intensity of the introduced light. The collected data sets are processed using an imaging algorithm. The imaging algorithm calculates the blood volume of the examined tissue for each source-detector combination for each data set. The imaging algorithm can also calculate the oxygenation of the examined tissue for each source-detector combination.

The blood volume or oxygenation images can be subtracted from "model" images. The blood volume image can be subtracted from the oxygenation image to create congruence data (further described below) to localize and characterize a tissue anomaly. The imaging algorithm may also create an image using the differential image data sets. Prior to creating the image, an interpolation algorithm is employed to expand the differential image data set, containing 16 (4x4) data points, to an imaging data set containing 32x32 image points.

Alternatively, the computer uses a back projection algorithm known in computed tomography (CT) modified for light diffusion and refraction and the banana like geometry employed by the optical imaging system. In the optical back projection algorithm, the probabilistic concept of the "photon migration density" replaces the linear relationship of ballistically transmitted X-rays, for the beam representing pixels. The photon migration density denotes a probability that a photon introduced at the input port will occupy a specific pixel and reach the detection port. For different types of tissue, the phase modulation spectrophotometer provides the values of the scattering and absorption coefficients employed in the probability calculations. (These values are determined as described in U.S. Patent 5,402,778, which is incorporated by reference) In the image reconstruction program, the probability is translated into a weight factor, when it is used to process back projection. The back projection averages out the values of information that each beam carries with the weighting in each pixel. The specific algorithms are provided in U.S. Pat. 5,853,370 issued on Dec. 29, 1998.

A method for correcting blurring and refraction used in the back projection algorithm was described by S.B. Colak, H.Schomberg, G.W.'t Hooft, M.B. van der Mark on March 12, 1996, in

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"Optical Back projection Tomography in Heterogeneous Diffusive Media" which is incorporated by reference as if fully set forth herein. The references cited in this publication provide further information about the optical back projection tomography and are incorporated by reference as if fully set forth herein.

5   Referring to Fig. 6, in another embodiment, amplitude cancellation imaging system 200 uses optical module 14 shown in Fig. 6A. In this arrangement, four centrally located light sources S1, S2, S3, and S4 and 21 detectors D1, D2, ..., D21 provide a multiplicity of symmetric photon migration paths for each source. For example, source S1 is turned ON for a period in the range of 10^{-6} sec to 0.1 sec. The source emits non-modulated light into the examined tissue.

10   Symmetrically located detectors D1 and D11 are ON simultaneously to collect introduced photons migrating over substantially symmetric paths. For symmetrical tissue conditions, detectors D1 and D11 detect light of the same intensity, and thus the differential signal is zero, i.e., the detected amplitudes are canceled. Imaging system 200 collects the differential data for a multiplicity of symmetric photon migration paths and generates an image of the examined tissue.

15   Imaging system 200 may collect optical data for several wavelengths and generate blood volume images and blood oxygenation images for the examined tissue. Amplitude cancellation imaging system 200 may also use a second identical optical module 14 placed to examine a symmetrical tissue region, or a symmetrical organ, for example, the two modules may be positioned to examine the right and left lungs. The blood volume images or the blood oxygenation images

20   collected for the two symmetric tissue regions may be subtracted to provide a differential image, which will further emphasize a tissue abnormality located in one tissue region.

Alternatively, the amplitude cancellation imaging system uses light modulated at frequencies in the range of 0.1 kHz to 100 kHz. The system employs the above-described algorithm, but the light sources emit frequency modulated light and the detectors, each connected

25   to a lock-in amplifier, detect light modulated at the same frequency. This lock-in detection may further increase the signal to noise ratio by eliminating external noise. The detected light intensities are processed the same way as described above to image the examined tissue.

Figs. 7, 7A and 7B show different embodiments of a cooling module used with a broad band light source or light guides, where these are positioned close to the skin. The broad band

30   light sources or light guides may create heat trapped close to the skin and thus uncomfortable temperature. Fig. 7 depicts a cooling module 230, which surrounds light sources 232A and 232B. Cooling module 230 includes a fan 234 and a set of air passages 236. In a similar design,

two fans are juxtaposed on each side of one or more light bulbs to form an "open frame" so that the fans blow not only upon the light sources, but upon the skin itself. The cooling module enables a power increase on the light sources, but no increase of heat upon the skin itself, which remains under comfortable conditions.

Fig. 7A depicts a cooling module 240 for cooling light guides. Light guides 242 deliver light and heat to the skin. A cooling ring 244 includes an air inlet 246 and a set of air passages 248 (or jets) for providing air flow to the irradiation location. Fig. 7B depicts a cooling module 250 constructed to air cool a light barrier 252. Light barrier 252 has similar optical properties as the light barrier described in the PCT application PCT/US92/04153 (published on November 26, 1992 as WO 92/20273), which is incorporated by reference. This embodiment utilizes the advantages of the light barrier and enables the use of higher light intensities. Cooling module 250 includes air inlets 252A and 252B, which provide air to a set of conduits and openings that deliver air to the skin near light source 254. Compressed air may also be used.

The safety regulations for delivering continuous otherwise non-coherent light of high intensities to the skin often depend on the temperature rise of the skin itself. For examination of large tissue volumes or deep tissues (i.e., where there is a large separation between the optical input and optical detection ports) relatively large light intensities are needed. Under conditions of prolonged even low level illumination, the skin may become uncomfortably warm and may blister. However, the erythemic effects are much smaller in the NIR, where the delivered heat is a factor, than they are in UVA and UVB, where cancer-producing damage may occur (but is not known for the NIR). The effect of the cooling air is not just convection of warm air away from the skin, but it enhances the evaporation of perspiration from the skin. Thus, as soon as the skin temperature rises and perspiration is initiated, greatly enhanced cooling is obtained with the forced air increasing the evaporation.

Referring to Fig. 8, an amplitude cancellation imaging system 260 is used instead of optical systems 15, 45, 100, 150, or 202. Dual wavelength amplitude cancellation imaging system 260 is connected to optical module 14, shown in Figs. 1B and 2B, which now includes four 750 nm laser diodes S_1, S_2, S_3, and S_4, four 830 nm laser diodes S_{1a}, S_{2a}, S_{3a}, and S_{4a}, and twenty-one silicon diode detectors D_1, D_2, ..., D_{21}. Each detector is connected to a preamplifier and an adjustable gain controller that may be used initially for calibration. The detector outputs are switched by a switch 262 and a controller 264 so that analog-to-digital converters 266 and 266a receive 750 nm and 830 nm data, respectively, from two symmetrically located detectors.

27

A computer 270 stores the detected values measured for the different combinations. The computer also generates images described below. Another type of amplitude detection circuit was described in Figures 11 through 13 and the corresponding specification of U.S. Patent 5,673,701, which is incorporated by reference as if fully set forth herein.

Also referring to Figs. 8A and 8B, the controller sequences an oscillator 261 so that each source emits a 50 μsec light pulse as shown in timing diagram 272. The system sequences through the various source/detector combinations in approximately one msec, and averages the imaged data over 8 sec to get a very high signal to noise ratio. Fig. 8A. shows the circuit configuration for one element of imaging system 260, i.e., 754 nm sources S_1, S_2 and 830 nm sources S_{1a}, S_{2a}, and two symmetrically positioned detectors D_3 and D_{11}, also shown in Fig. 2A. The light intensities detected for the symmetrical locations are subtracted in a digital or analog way. The computer stores all differential data, detected for the two wavelengths, for generating tissue images.

Fig. 8C shows diagrammatically a single channel 260A of the time multiplex imaging system 260. Detector D_1 detects light emitted from light source S_1 emitting light pulses of the duration of about 50 μsec. The detector signal is amplified and provided to a sample-and-hold circuit and filter. Detector D_1 is a silicon diode detector that has the detection area of about 4 X 4 mm and includes a pre-amplifier. The filtered signal 272 is provided to an AGC 274, which adjusts the amplitude of the signal based on a control signal from a personal computer. The personal computer has normalization amplitudes for the individual source-detector combinations.

Amplitude cancellation imaging system 260 is normalized on a tissue model by detecting signals for the individual source-detector combinations and appropriately normalizing the detected signal using the AGC control. The individual normalization/calibration amplitudes form a baseline image that is stored in the computer. As described above, the baseline image may also be acquired on a symmetric tissue region, such as the contralateral kidney or a symmetric tissue region of the same organ for internal tissue examination. The normalization process can be repeated several times to account for drifts in the individual elements. During the measurement process, the personal computer can adjust the gain of each AGC 314 based on the calibration values that account only for the electronic drift. Then, the defected image is subtracted from the baseline image of the examined tissue. Alternatively, while collecting the measurement data on the examined tissue, the measurement image is subtracted from the baseline image to create the tissue image that includes any tissue in homogeneities such as a

tumor or bleeding. The sample-and-hold circuit maybe an analog circuit or the sample-and-hold function, including the filtering, may be performed digitally.

Fig. 8D shows diagramatically an amplitude cancellation imaging system employing a frequency multiplex method. Amplitude cancellation system 300 includes 21 oscillators 302 operating a frequencies in the range of 1 kHz to 100 kHz. Each oscillator 302 drives a light source 304 (for example, a laser diode or LED), which emits an intensity modulated light into the examined tissue. Each light detector 306 (for example, a photomultiplier, an avalanche photodiode PIN detector or a silicon detector) detects the intensity modulated light and provides a detector signal to an amplifier 308. The amplified detector signal is provided to a processing channel 310, which includes a band pass filter 312, an AGC 314, a lock-in amplifier 316, and a filter 318. Filter 312 filters the detector signal, and AGC 314 adjusts the amplitude according to the input signal from a personal computer. Lock-in amplifier 316 receives the amplified signal 315 and a reference signal 320 from oscillator 302. Lock-in amplifier 312 provides amplitude signal 317 to filter 318. Processing channel 310 may be an analog channel or a digital channel.

In the amplitude cancellation system 310, all light sources emit light at the same time into a selected tissue region. Each light source is modulated at a distinct frequency in the range of 1 kHz to 100 kHz. In order to resolve the modulated light signals and attribute them to the individual light sources, the oscillators operate at frequencies 1 kHz, 2 kHz, 4 kHz, 8 kHz, 16 kHz, ... Filters 312 and 318 are designed to provide only the detection signal from a selected light source, and lock-in amplifier 312 provides the amplitude of the signal at the selected frequency. Frequency multiplex system 300 is calibrated the same way as the time multiplex system 260, and the normalization/calibration amplitude values are also stored in the personal computer. The images are processed as described above.

All above-described optical systems will achieve a higher spacial resolution of the imaged tissue by increasing the number of sources and detectors. Furthermore, the sources and detectors may form various 1 dimensional, 1.5 dimensional, or 2 dimensional arrays as described in the above-referenced documents.

Before examination of a selected tissue region, the imaging system is first calibrated on a tissue model. The model data for different source-detector combinations is stored in a digital form. Alternatively, the model calibration may be performed by adjusting the detector gains prior to the tissue measurements. During the examination, the optical probe is placed over a designated body area, for example, a selected abdominal, thoracic, back or pelvic area of the

body to target a selected organ. Two optical probes may be used to examine symmetrical organs. The images can be also acquired by taking advantage of *a priori* information obtained by X-ray tomography, an MRI or ultrasonic scan. The optical images are created using a back projection algorithm with or without correction for non-ballistic photon propagation (i.e., tissue absorption or scattering). The images may be displayed in the format of the tissue data minus the model data, or the right organ tissue data minus the left organ tissue data, for each wavelength (e.g., 750 and 830 nm).

The optical images may also be processed to image blood volume and blood oxygenation of the examined tissue. The blood volume image is the sum of 0.3 times the 750 nm data and 1.0 times the 830 nm data. The blood deoxygenation image is the difference of the 750 nm and the 830 nm data. The above coefficients, related to the absorption of oxy- and deoxy-hemoglobin, were derived from blood tests in model systems. The images have the highest specificity and sensitivity for symmetric organs or tissue regions, where the contralateral tissue region data is used as a baseline and both the blood volume data and the hemoglobin deoxygenation data is imaged and positionally compared.

Fig. 1C illustrates a pair of sources illuminating a pair of detectors with photon migration patterns intercepted by the head of a fetus. The distance between the sources and the detectors is 10 cm. The optical module is placed on the skin of the abdomen 350 in the pelvic area of woman 8 (Fig. 1). The location of the optical module may be determined by a prior ultrasound scan or by taking several optical images at varying locations. At the suitable position, most of the source - detector combinations generate banana patterns that penetrate the abdominal wall 352 and interine wall 354 and intercept different portions of the head 356 of the fetus 358. Some of the patterns are transmitted through the spaces not containing the head, which therefore provide a background signal. The background signal can be used to image the margin of the head.

Referring to Figs. 1A and 4, optical module 14 may be used with optical system 45. Optical module 14 has 9 sources and 4 detectors to be placed at distances of 9 cm apart on a 35 x 23 cm pad. (Optical modules of different sizes may be used at different stages of the pregnancy.) Imaging system 45 achieves phase cancellation in the detector, as described above. That is, two sources at the same wavelength, modulated with 0 phase and 180° phase, simultaneously illuminate the symmetrically located detector. Most of the banana-shaped optical patterns pass through the head and are thus appropriately perturbed by the absorption/scattering of the baby

head. The imaging system uses a back projection algorithm to construct an image of the baby's
head with signals at both wavelengths. Thus, the processor can generate images of the blood
volume and the blood deoxygenation of the examined region of the head of the fetus. These
images may be used for routine examination of the fetus during pregnancy. These images may
also be used for long term monitoring of the fetus, where the optical module is worn by the
pregnant woman. The above-described systems can not only image the head, or other parts of
the fetus, they can also measure the blood oxygenation and non-invasively characterize the
tissue of the fetus.

Alternatively, the above described imaging system may be used for monitoring during
labor. After detecting the position of the fetal head, the optical module may be strapped in one
location since the head is usually fixed in the cervix area. The imaging system would also
provide the pulse rate of the fetus using the pulse oximetry technology. (See, for example, U.S.
Patents 5,218,962; 4,869,254; 4,846,183; 4,700,708; 4,576,173 and the references cited therein)
Based on the optical data (e.g., blood volume and oxygenation) and the detected pulse rate, the
attending obstetrician can decide at any time whether to pursue vaginal delivery of the fetus or
perform a C-section.

Prior to conducting the NIR transabdominal measurement, an ultrasound exam may be
performed to determine the position of the fetal head, the placenta and the distance between the
ultrasound transducer and the fetal brain. The optical probe is then placed on the maternal
abdomen right above the pubic bone in a way that the sources and the detectors symmetrically
straddled the location on the skin right above fetal brain. If the average distance between the
surface of the fetal brain and the ultrasound transducer is about 2.5 cm, the optimal source and
detector separation is about 10 cm in order to aim for a penetration depth of approximately 5 cm.
To examine just the superficial maternal abdominal and uterine layers in a complementary
measurement, the source and detector separation of 4 cm may be used. Prior to the
measurement, a Doppler transducer and a pressure-sensitive monitor are attached to the maternal
abdomen to monitor the fetal heart rate and uterine pressure, respectively. The optical apparatus
calibration is performed when the fetal heart rate and uterine pressure are at a stable base line
rate.

The optical measurement is synchronized with the fetal heart rate and uterine pressure
using 760 nm and 850 nm wavelengths. The duration of the measurement may be approximately
30 minutes (duration of the antepartum NS). The optical density (O.D.) at each wavelength was

calculated in order to account for the different base line calibration signals (I_o) at the two wavelengths for each patient. The incremented absorbance in ΔO.D. was calculated using the following set of equations:

$$\Delta O.D. = \log\left(\frac{I_o}{I_{850nm}}\right) - \log\left(\frac{I_o}{I_{760nm}}\right)$$

$$\Sigma O.D. = 0.1 \times \log\left(\frac{I_o}{I_{760nm}}\right) + \log\left(\frac{I_o}{I_{850nm}}\right)$$

where Δ O.D. is a measure of blood oxygenation, Σ O.D. is a measure of blood volume and I_{760nm} and I_{850nm} are the re-emitted signals at 760 and 850 nm, respectively.

To verify that the probe collects photons migrating trans-abdominally through the fetal head, the optical measurements are conducted in conjunction with vibro- acoustic stimulation of the fetus. Vibro- acoustic stimulation of the human fetus by means of artificial electronic larynx can reduce the false-positive and false-negative rates of NST. Vibro- acoustic stimulation is been used primarily to elicit accelerations in non-reactive fetal heart rates; this is considered a positive sign of fetal well being. Furthermore, the use of vibro acoustic simulation has been demonstrated to be a reliable means to achieve fetal heart rate activity.

A variety of tests and demonstrations have been put forward, each of which is consistent with the presence of a blood containing object within the uterus and in the position indicated by ultrasound. A quantitative validation the optical data is performed on the model of the near term maternal abdomen. Taking into account that the position of the model fetus should be matched with the *in vivo* fetus, ultrasound guidance permits matching of the fetal position in both systems. This principle of successive substitutions and better approximations of the model to the *in vivo* system affords a viable approach to instrumentation development and improvement.

The model uses a hemispherical spun copper mold into which a latex liner is poured in a thin uniform layer. This latex liner will simulate the sponge rubber pad in which the source and detectors are approximately located. An elastomer layer of low $\mu_a = 0.2$ cm^{-1} and $\mu_s' = 10$ cm^{-1} is next poured into the model for thickness of 5 cm to simulate an adipose layer (a skin layer). A highly scattering material $\mu_a = 0.1$, $\mu_s' = 10$ is poured into the model to simulate the musculature of the abdomen and of the uterus. This casting is held in place at the required thickness by an

inner hemispherical shell. When solidified, the model is moved from the spun copper hemisphere and filled with water with small amounts of a scatterer (Intralipid) to simulate the turbid placental fluid.

The source/detector combinations are assembled on the outside of the model and observations are taken with and without a grapefruit sized object. A cellophane vessel with blood at 50 micromolar concentration which can be in the oxygenated or deoxygenated state. A number of studies can be carried out with the model head present and absent and filled with blood of various concentrations and oxygenation states, the latter being pumped through the model. The model consists of intralipid scattering factor $u_s' = 10$ cm^{-1} $\mu_a = 0.01$ cm^{-1} filled with hemoglobin. This material is pumped through the model in the initial oxygenated state and upon the addition of yeast, in the deoxygenated state. Intermediate values of oxygenation are obtained without yeast by supplying the blood reservoir with oxygen/nitrogen values giving saturation between 5 and 95%. The following can be performed to optimize the system:

The concentration of blood can be varied from the standard hematocrit of 70 micromolar to 30 and 110 micromolar and the signal intensity for short and long pathlengths for the medial position of the simulated head are plotted. The oxygenation of hemoglobin at the three hematocrit are varied from 30% to 50% to 70% at the three blood concentrations mentioned above. Cross correlation plots of different blood concentration and blood oxygenation are made. Finally, yeast can be added to the blood model and transitions from the normoxic value of 70, 50, 30 and on to 0 are made in the medium position to test the validity of the arbitrary calibration of the probe.

The optical properties and thickness of the uterine tissue layer is varied and the changes in oxygenation of the fetal brain model can be evaluated for a fixed 50 μM concentration of hemoglobin. This can be used to determine the sensitivity and detection limits of the NIR signal to changes in oxygenation as a function of uterine optical properties and thickness as well.

The head can be placed 3 cm from the surface and translated parallel to and perpendicular to the long axes of the source detector combinations. The signal intensity is then plotted for short and long pathlengths. Furthermore, an imaging device can be designed based upon the modulation of the head position and the responses of the probes.

In addition to the rectangular probes shown in Figs. 1A and 1B, the above-described systems can use a concentric circle probe providing a wide variety of short and long paths, source-detector combinations afforded by the concentric circles of light sources and detectors.

33

The optical probe with the concentric circles may use all light sources in a particular circle to illuminate the abdomen and the light detection can be localized in a single detector, or concentric circles of detectors. Imaging with at least three concentric circles of sources and detection can set up as the initial imaging system. When using the above-described amplitude cancellation and/or phase cancellation systems, the concentric circles probe defines the contours of fetal head and possibly the body as well.

As shown in Figs. 2, 2A and 2B, optical modules 12 or 14, located on the back of a subject, are used for *in-vivo* transabdominal or transthoracic examination of internal tissue. Any of the optical systems described in connection with Figs. 3 through 8D may be connected to one or several optical modules 12 or 14 to collect optical data from a tissue region of interest.

The optical system may generate single wavelength or multiple wavelength data sets of the examined tissue region, wherein the employed wavelength is sensitive to absorption or scattering by a tissue constituent (e.g., an endogenous or exogenous pigment, tissue cells, chemical compounds) or is sensitive to structural changes the examined tissue region. The optical data sets may represent tissue absorption, tissue scattering, or both. The optical data sets system may also generate blood volume and hemoglobin deoxygenation images, or images of any other tissue constituent, based on multiple wavelength optical data. A processor may use different image processing and enhancing algorithms known in the art. The processor may correlate several images to detect a suspicious tissue mass and to characterize the detected mass. The correlation includes determining congruency of the structures detected in different images. The processor may employ different types of combined scoring, based on several optical images alone or in combination with X-ray mammography, ultrasound examination, or *f*MRI, to characterize a suspicious tissue mass.

The blood volume and hemoglobin deoxygenation images provide an important tool for characterizing a suspicious anomaly in the examined tissue. While the blood volume and hemoglobin deoxygenation images, as well as the single wavelength images, are useful in locating an abnormal tissue region, these images are also used to characterize the metabolism or pathology of the suspicious tissue anomaly. Specifically, an increased blood volume signal is observed due to the increased vascularity of a tumor as a consequence of angiogenetic factors. These factors include actively metabolizing regions and necrotic/apoptotic regions of the tumor. On the other hand, the hemoglobin deoxygenation signal is related to metabolic intensity. That is, the balance between oxygen delivery and oxygen uptake, which in tumors is usually balanced

in favor of oxygen uptake exceeding oxygen delivery. The increased oxygen uptake occurs particularly for those tumors that are aggressively growing, and may as well be metastatic.

By selecting an appropriate wavelength, or several wavelengths, sensitive to an optically active tissue property, the imaging system can non-invasively characterize a tissue anomaly. The above-mentioned wavelengths are sensitive to hemoglobin and hemoglobin oxygenation, but other wavelengths sensitive to absorption by any tissue constituent may be used. Furthermore, an optical contrast agent (e.g., cardiogreen, indocianine green) may be injected intravenously. The imaging system will then use a wavelength sensitive to the administered contrast agent. The regions of increased blood volume will also have a higher content of the contrast agent.

Alternatively, differences in tissue scattering may be imaged. Due to differences in the optical refractive index, different types of tissue and different tissue solutes scatter light differently. The above-described imaging systems are also sensitive to scattering changes. The imaging system may use a wavelength that does not exhibit absorption changes for different types of tissue or different tissue solutes, but exhibits differences in scattering.

Non-invasive characterization of tissue may be performed by combining the data from the above described images. For example, a two dimensional data chart may display blood volume (i.e., vasculogenesis) vs. blood deoxygenation (i.e. hypermetabolism) for a "suspicious" tissue region using the model data as a reference, using a symmetrical tissue region as a reference, or using a symmetrical organ data as a reference.

The imaging system performs the following tissue characterization by co-registration of several images. In principle, vasculogenesis (blood volume) and hypermetabolism (tissue hypoxia) occur in similar and often identical tissue volumes. Thus, the two images would show pronounced structures in the same location. The vascular volume is represented by the blood volume signal. The imaging systems evaluates the congruence of the two image structures in order to locate a suspicious tissue region. The first step is the normalization of the two images to equalize the maximum signals. A computer program selects the area and obtains the integrated value for the spatial congruence residual and for the blood volume signal. Then, subtraction pixel-by-pixel gives an image that provides a residual value used to estimate the congruence of the two shapes obtained from the blood volume and deoxygenation images. A simpler procedure is to take the maximum value of the difference and divide it by the maximum value of the normalized value for the two images.

Referring to Fig. 9, a "four" dimensional graph may be used to summarize images of

suspicious regions (Here Fig. 9 is only a proposed technique for data evaluation and does <u>not</u> show actual tissue data). The blood volume (measured in volts) is plotted on the abscissa and deoxygenation (measured in volts) is plotted on the ordinate. The measured size of a suspicious mass is depicted as a circle diameter and the percentage congruence between the blood volume image and the deoxygenation image of the suspicious mass can be shown using a color scale. The percentage of congruence signals may be given in a color scale based on the following formula:

$$1 - \left(\frac{maximum\ overlap\ residual}{maximum\ blood\ volume\ signal} \right) \times 100$$

The "four" dimensional diagram is based on the following:

1. The size of the image of a suspicious mass (plotted as one half its longest dimension).
2. The congruence of blood volumes and blood deoxygenation in color.
3. The blood volume in the congruent region measured in volts (scale of the abscissa).
4. Blood deoxygenation in the congruent region in volts (scale of the ordinate).

The four-dimensional nature of Fig. 9 permits the assignment of sensitivity and specificity according to the signal strength of blood volume data and the signal strength of deoxygenation data. I divided the region of signals in Fig. 9 into four zones. Zone I was defined for blood volume values above about 2.4 V and deoxygenation values above about 1.4 V. Zone II, located below Zone I, was defined for blood volume values above about 1.7 V and deoxygenation values above about 0.75 V. Zone III, located below Zone II, was defined for blood volume values above about 1.3 V and deoxygenation values above about 0.2 V. Zone IV was located below Zone III. Zones III and II may likely include cancerous masses which are expected to provide high blood volume and deoxygenation signals.

The image structures to be evaluated in the optical images may be selected using X-ray, ultrasound or MRI data. Alternatively, image structures may be based upon "suspicious mass" guidance only, using the contralateral tissue data as a reference, or using the model data as a reference. The use of the contralateral tissue (i.e., the symmetric tissue) reduces the signals from abnormal tissue (e.g., non-cancerous tissue), but the measurement on the symmetric tissue is not always feasible.

Additional embodiments are within the following claims.

Claims:

1.   An optical method for *in vivo*, non-invasive, transabdominal examination of fetal tissue comprising:

providing an optical module including an array of optical input ports and detection ports located in a selected geometrical pattern that provide a multiplicity of photon migration paths inside the uterus of a pregnant female subject;

placing said optical module on the exterior of the abdomen of the pregnant female subject;

introducing visible or infrared light from at least one said optical input port into the uterus and receiving photons that have migrated in the uterus to at least one of said detection ports;

detecting said received photons by at least one optical detector optically coupled to said least one detection port;

controlling said introducing and detecting steps to collect optical data corresponding to photons of light that have partially migrated inside a fetal tissue region; and

processing said optical data to characterize the fetal tissue region.

2.   The optical method of claim 1 wherein said processing includes determining hemoglobin oxygenation of said fetal tissue.

3.   The optical method of claim 1 wherein said processing includes determining a pulse rate of the fetus.

4.   The optical method of claim 1 wherein said controlling step includes collecting said optical data corresponding to photons that have partially migrated inside brain tissue of the fetus.

5.   The optical method of claim 1 wherein said placing step includes moving said optical module on the exterior of the abdomen to relocate said photon migration paths inside the uterus so that said optical data correspond to photons that have partially migrated inside brain tissue of the fetus.

6.   The optical method of claim 1 further including locating the head of the fetus by
using an ultrasound system and then, based on said locating, performing said placing of said
optical module on the exterior of the abdomen to position said photon migration paths inside the
uterus so that said optical data correspond to photons that have partially migrated inside brain
tissue of the fetus.

7.   The optical method of claim 4, 5 or 6 wherein said processing includes
determining hemoglobin oxygenation of said brain tissue.

8.   The optical method of claim 4, 5 or 6 wherein said processing includes
determining a pulse rate of the fetus.

9.   The optical method of claim 4, 5 or 6 wherein said processing includes evaluating
said brain tissue.

10.   The optical method of claim 4, 5 or 6 wherein said processing includes creating
an image of said brain tissue.

11.   The optical method of claim 4, 5 or 6 wherein said processing includes
forming at least two data sets, a first of said data sets representing blood volume in said brain
tissue and a second of said data sets representing blood oxygenation said brain tissue; and the
method further including correlating said first and second data sets to detect abnormal tissue in
said brain tissue.

12.   The optical method of claim 11 wherein said processing includes creating images
blood volume in said brain tissue and blood oxygenation in said brain tissue.

13. An optical apparatus for *in vivo*, non-invasive, transabdominal examination of fetal
tissue comprising:
        an optical module including an array of optical input ports and detection ports located in
a selected geometrical pattern to provide a multiplicity of photon migration paths inside the
uterus, each said optical input port being constructed to introduce visible or infrared light emitted

from a light source, each said optical detection port being constructed to receive photons of light that have migrated from at least one of said input ports and provide said received light to a light detector;

a controller constructed and arranged to control operation of said light source and said light detector to detect photons that have migrated over at least one of said photon migration paths inside fetal tissue; and

a processor connected to receive signals from said detector and arranged to characterize the fetal tissue region.

14.   The optical apparatus of claim 13 wherein said processor is further arranged to determine hemoglobin oxygenation of said fetal tissue.

15.   The optical apparatus of claim 13 wherein said processor is further arranged to determine a pulse rate of the fetus.

16.   The optical apparatus of claim 13 wherein said controller and said processor are arranged to evaluate said optical data and subsequently control operation of said light source and said light detector to collect additional optical data corresponding to photons that have partially migrated inside brain tissue of the fetus.

17.   The optical apparatus of claim 13 wherein said optical module is constructed for placement on the abdomen based on locating the head of the fetus by an ultrasound system so that said optical data correspond to photons that have partially migrated inside brain tissue of the fetus.

18.   The optical apparatus of claim 16 or 17 wherein said processor is arranged to determine hemoglobin oxygenation of said brain tissue.

19.   The optical apparatus of claim 16 or 17 wherein said processor is arranged to determine a pulse rate of the fetus.

20.   The optical apparatus of claim 16 or 17 wherein said processor is arranged to

create an image said brain tissue.

21.   The optical apparatus of claim 16 or 17 wherein said processor is arranged to create images blood volume in said brain tissue and blood oxygenation in said brain tissue.

22. An optical system for *in vivo*, non-invasive examination of internal tissue of a subject comprising:

an optical module including an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue, each said optical input port being constructed to introduce visible or infrared light emitted from a light source, each said optical detection port being constructed to receive photons of light that have migrated in the examined tissue region from at least one of said input ports and provide said received light to a light detector;

a controller constructed and arranged to control operation of said light source and said light detector to detect light that has migrated over at least one of said photon migration paths; and

a processor connected to receive signals from said detector and arranged to form at least two data sets, a first of said data sets representing blood volume in the examined tissue region and a second of said data sets representing blood oxygenation in the examined tissue region; said processor being arranged to correlate said first and second data sets to detect abnormal tissue in the examined tissue region.

23.   The optical system of claim 22 wherein said second data set includes hemoglobin deoxygenation values.

24.   The optical system of claim 22 wherein said processor is arranged to form a third data set being collected by irradiating a reference tissue region.

25.   An optical system for *in vivo*, non-invasive examination of internal tissue of a subject comprising:

an optical module including an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an

examined region of the biological tissue, each said optical input port being constructed to introduce visible or infrared light emitted from a light source, each said optical detection port being constructed to receive photons of light that have migrated in the tissue from at least one of said input ports and provide said received light to a light detector;

a controller constructed and arranged to control operation of said light source and said light detector to detect light that has migrated over at least one of said photon migration paths; and

a processor connected to receive signals from said detector and arranged to form at least two data sets, a first of said data sets being collected by irradiating an examined tissue region of interest and a second of said data sets being collected by irradiating a reference tissue region having similar light scattering and absorptive properties as the examined tissue region, said processor being arranged to correlate said first and second data sets to detect abnormal tissue in the examined tissue region.

26.   An optical system for *in vivo*, non-invasive examination of internal tissue of a subject comprising:

an optical module including an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the biological tissue or a model representing biological tissue, each said optical input port being constructed to introduce visible or infrared light emitted from a light source, each said optical detection port being constructed to receive photons of light that have migrated in the tissue or the model from at least one of said input ports and provide said received light to a light detector;

a controller constructed and arranged to control operation of said light source and said light detector to detect light that has migrated over at least one of said photon migration paths; and

a processor connected to receive signals from said detector and arranged to form at least two data sets of two tissue regions, a first of said data sets being collected by irradiating an examined tissue region and a second of said data sets being collected by irradiating a region of a tissue model having selected light scattering and absorptive properties, said processor being arranged to correlate said first and second data sets to detect abnormal tissue in the examined tissue region.

27.   The optical system of claim 22 or 24 further including a second optical module including an array of optical input ports and detection ports located in a selected geometrical pattern to provide a multiplicity of photon migration paths inside an examined region of the tissue, each said optical input port being constructed to introduce visible or infrared light emitted from a light source, each said optical detection port being constructed to receive photons of light that have migrated in the examined tissue region from at least one of said input ports and provide said received light to a light detector; said processor being arranged to receive optical data from both said optical modules.

28.   The optical system of claim 22, 25 or 26 wherein said processor is arranged to correlate said first and second data sets by determining congruence between data of said two sets.

29.   The optical system of claim 28 wherein said processor is programmed to order said first and second data sets as two-dimensional images and to determine said congruence using said two-dimensional images.

30.   The optical system of claim 28 wherein said processor is programmed to order said first and second data sets as two-dimensional images and to determine said congruence using the following formula:

$$1 - \left(\frac{maximum\ \ overlap\ \ residual}{maximum\ \ selected\ \ tissue\ \ signal} \right) \times 100$$

31.   The optical system of claim 22, 23, 24, 25, 26, 27, 28, 29 or 30 wherein said processor is further arranged to determine a location of said abnormal tissue within the examined tissue region.

32.   The optical system of claim 22, 25 or 26 wherein said processor is adapted to produce from said data set an image data set by implementing an optical tomography algorithm.

33.   The optical system of claim 32 in which said optical tomography algorithm employs factors related to determined probability distribution of photons attributable to the scattering character of the tissue being imaged.

34.   The optical system of claim 22, 25 or 26 wherein said controller is arranged to   -
activate said source and said detector to obtain a first selected distance between said input and
detection ports and said processor is arranged to form said data set for said first distance.

35.   The optical system of claim 34 wherein said processor produces an image data set
from said data set formed for said first distance.

36.   The optical system of claim 34 wherein said controller further is arranged to
activate said source and said detector to obtain second distance between said input and detection
ports and said processor is arranged to form another data set for said second distance.

37.   The optical system of claim 32, 33, 34, 35 or 35 further including a display device
constructed to receive said image data set from said processor and to display an image.

38.   The optical system of claim 22, 25 or 26 constructed to introduce and detect
photons at two wavelengths selected to provide sensitivity to a tissue constituent.

39.   The optical system of claim 38 wherein said tissue constituent is an endogenous
pigment.

40.   The optical system of claim 39 wherein said endogenous pigment is hemoglobin.

41.   The optical system of claim 38 wherein said tissue constituent in an exogenous
pigment.

42.   The optical system of claim 41 in which said exogenous pigment is a selected
contrast agent.

43. An optical method for *in vivo*, non-invasive examination of internal tissue of a
subject comprising:

        providing an optical module including an array of optical input ports and detection ports
located in a selected geometrical pattern to provide a multiplicity of photon migration paths

inside an examined region of the tissue;

placing said optical module on the skin of the subject;

introducing visible or infrared light from at least one said optical input port into an examined tissue region and receiving photons of light that have migrated in the examined tissue region to at least one of said detection ports;

detecting said received photons by at least one optical detector optically coupled to said least one said detection port;

controlling said introducing and detecting steps to collect optical data corresponding to photons of light that have migrated between selected input and detection ports;

processing said optical data to form at least two data sets, a first of said data sets representing blood volume in the examined tissue region and a second of said data sets representing blood oxygenation in the examined tissue region; and

correlating said first and second data sets to detect abnormal tissue in the examined tissue region.
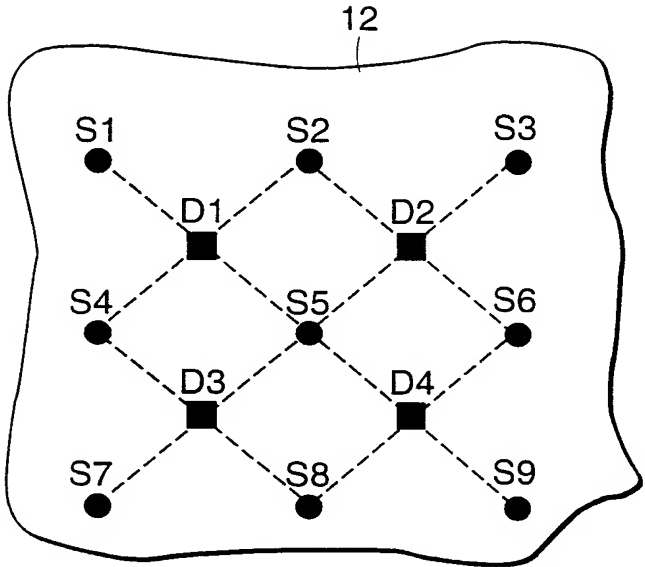
FIG. 1A
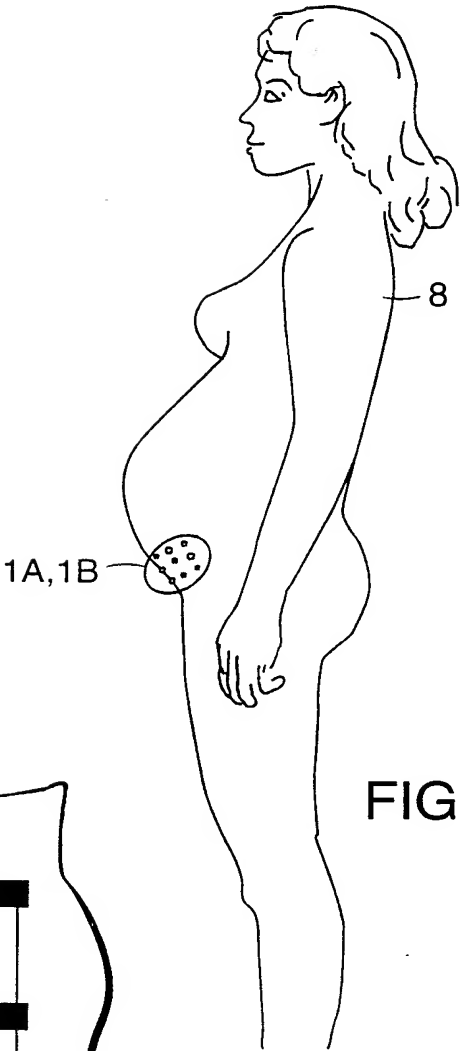
FIG. 1
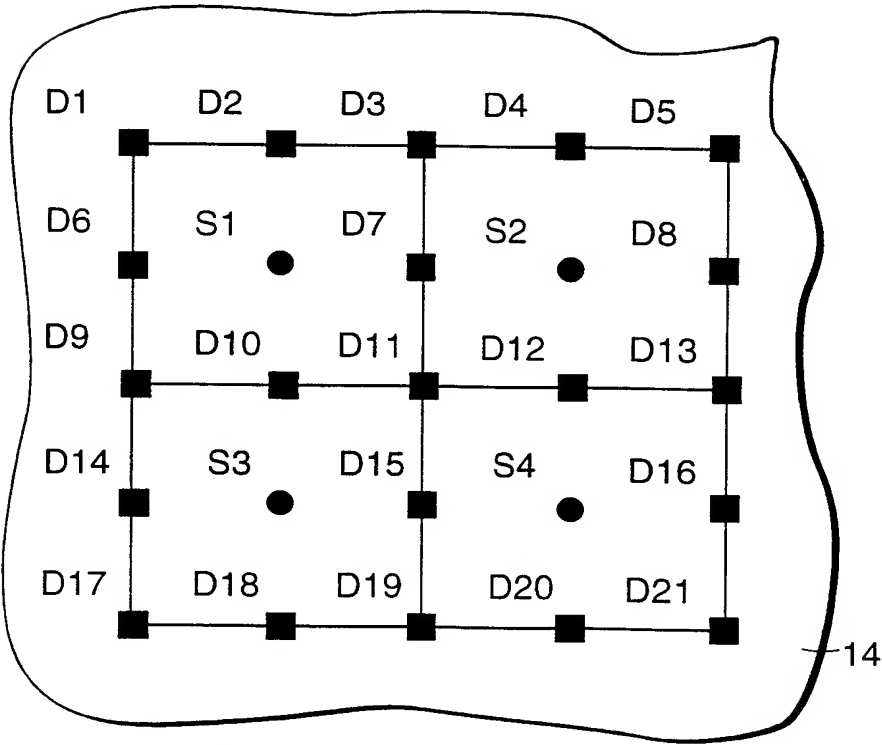
■ — DETECTOR
● — SOURCE: 750nm, 830nm

FIG. 1B
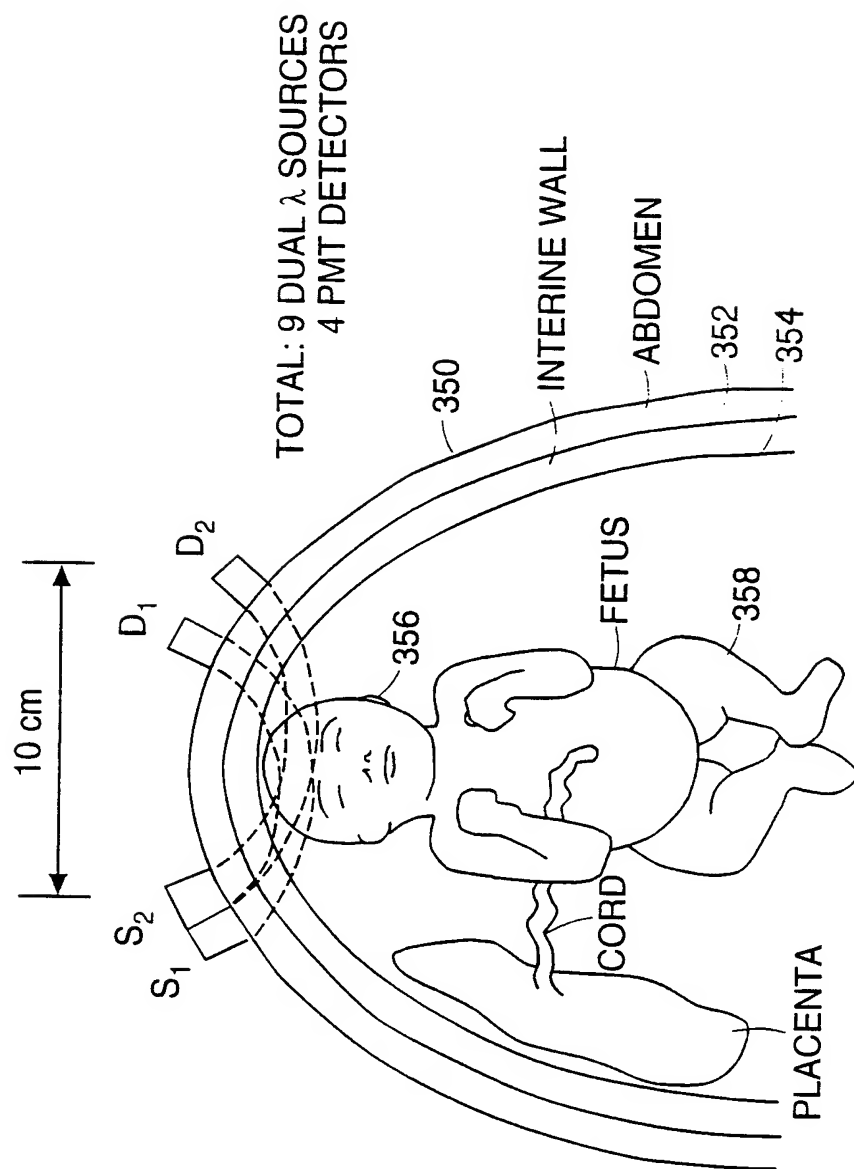
FIG. 1C
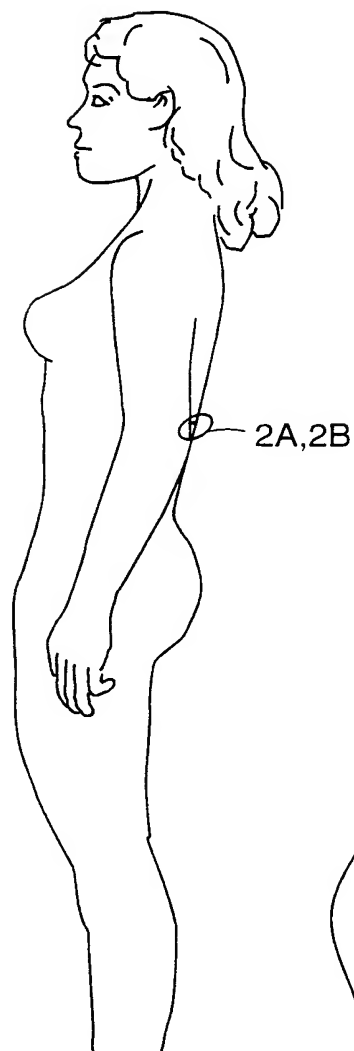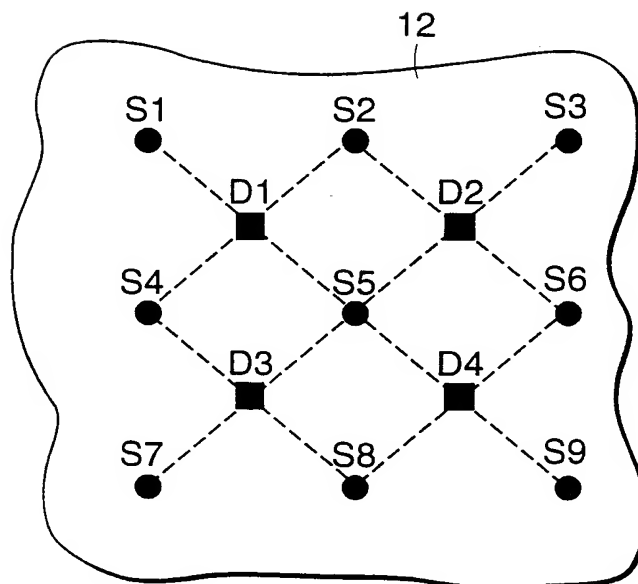
FIG. 2

FIG. 2A
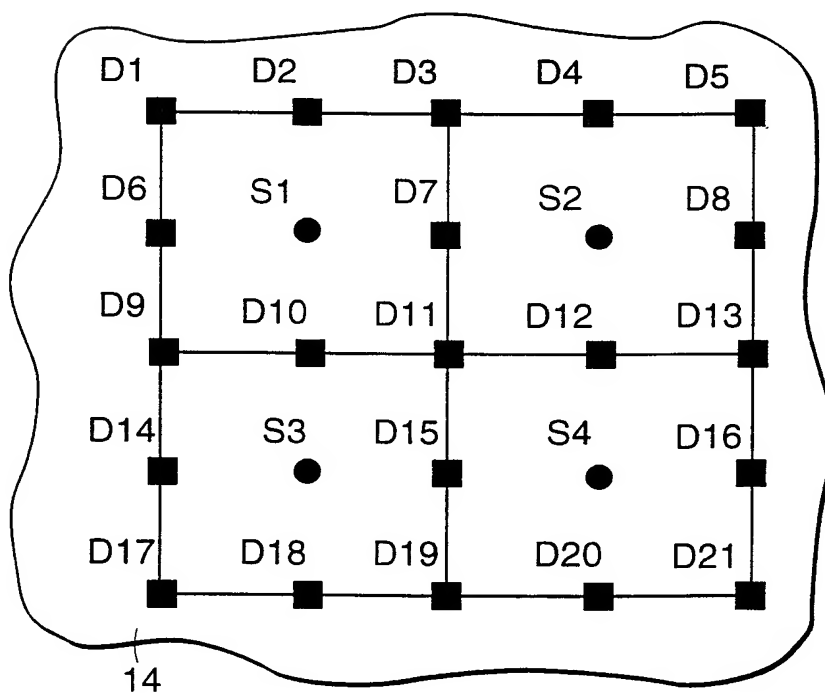
■ — DETECTOR
● — SOURCE: 750nm, 830nm

FIG. 2B

50 MHZ SINGLE WAVELENGTH PMS/PHASE ARRAY IMAGE SYSTEM
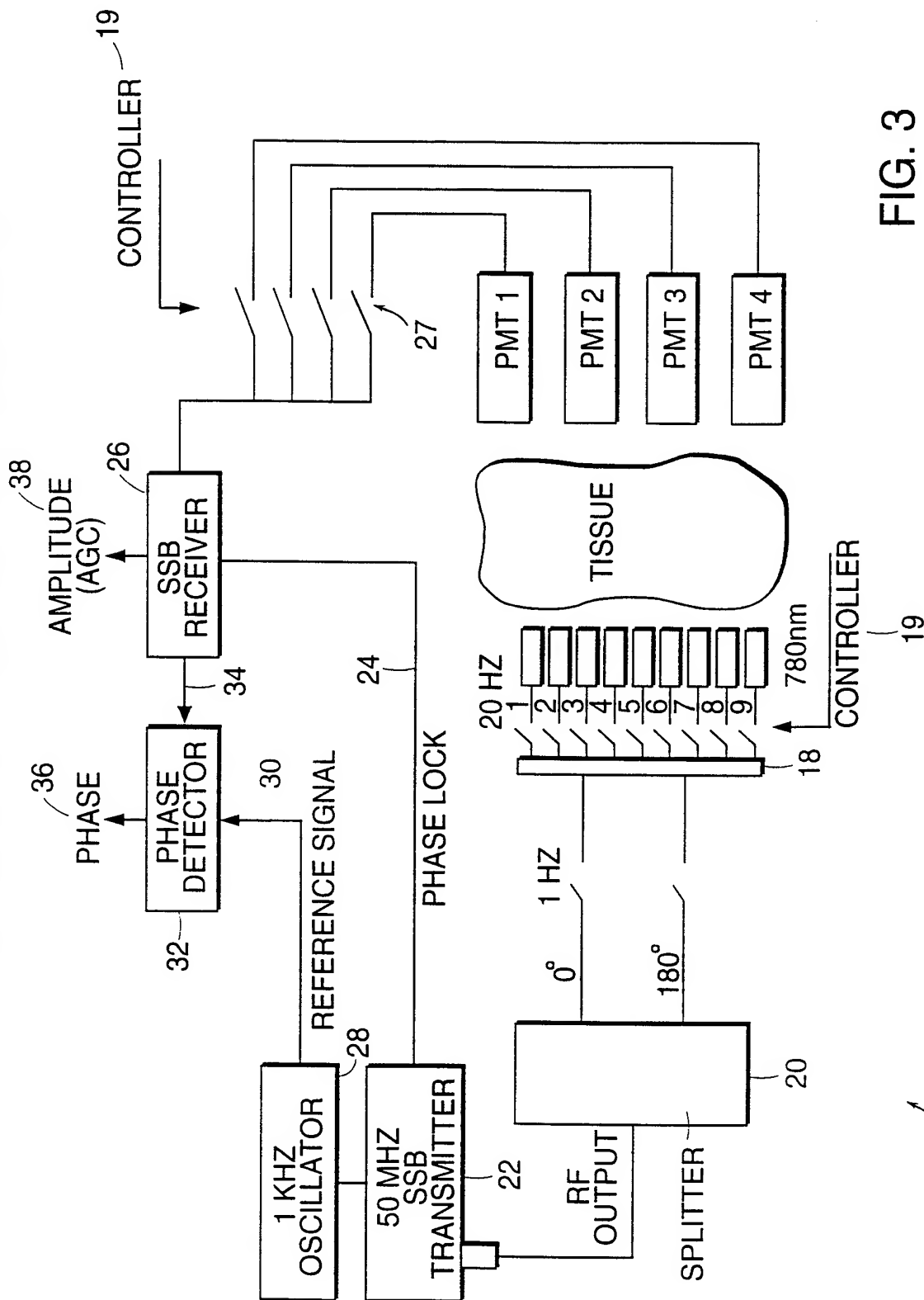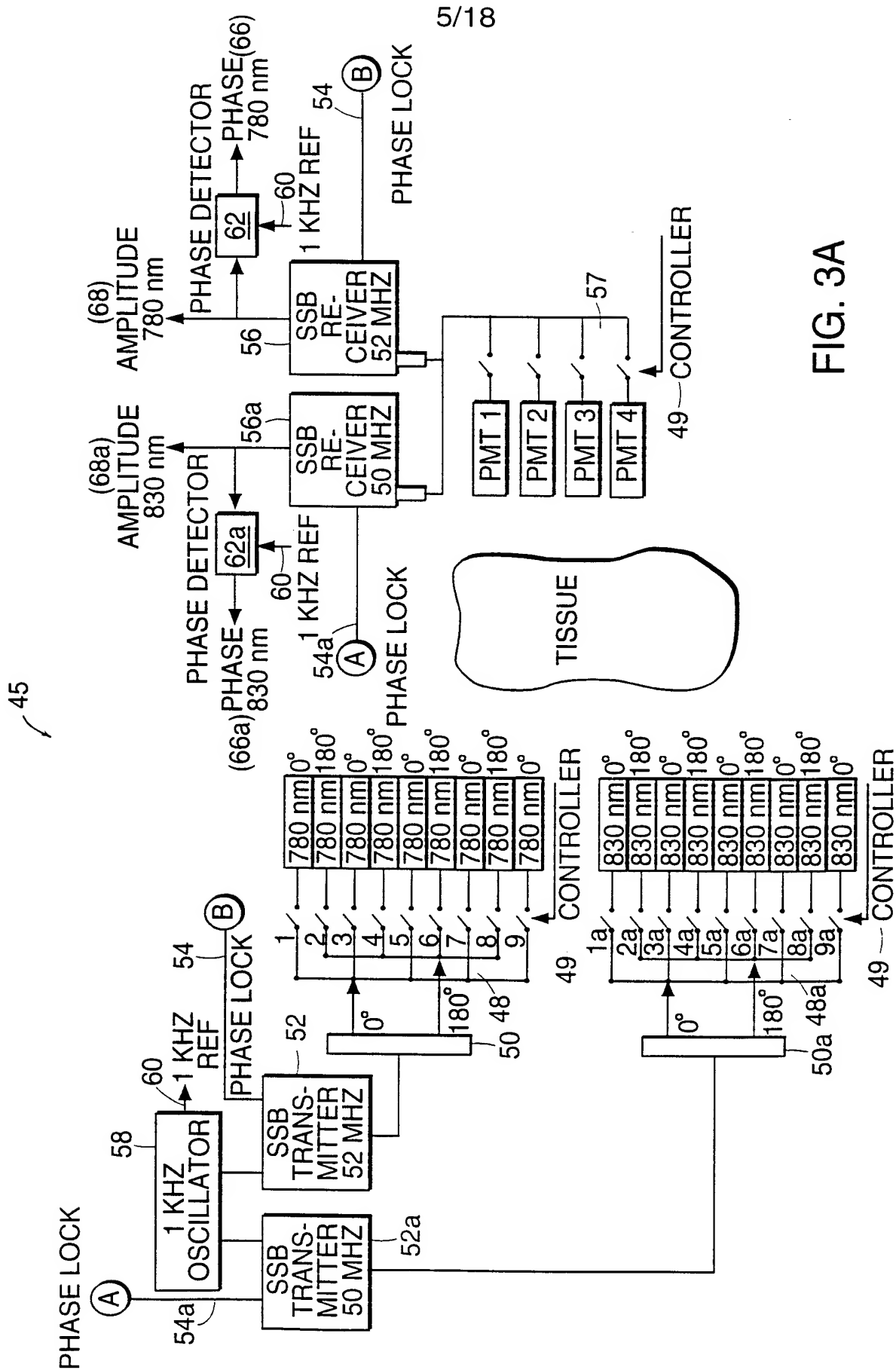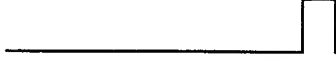
FIG. 3

FIG. 3A

SOURCES	DETECTORS
1, 2, 1a AND 2a	1
2, 3, 2a, AND 3a	2
4, 5, 4a, AND 5a	1
5, 6, 5a, AND 4a	2
7, 8, 7a, AND 8a	3
8, 9, 8a, AND 9a	4
4, 5, 4a, AND 5a	3
5, 6, 5a, AND 6a	4
7, 8, 7a, AND 8a	3

40

FIG. 3B

FIG. 4

$$\theta = TAN^{-1} \frac{I}{R}$$

$$A = \sqrt{R^2 + I^2}$$
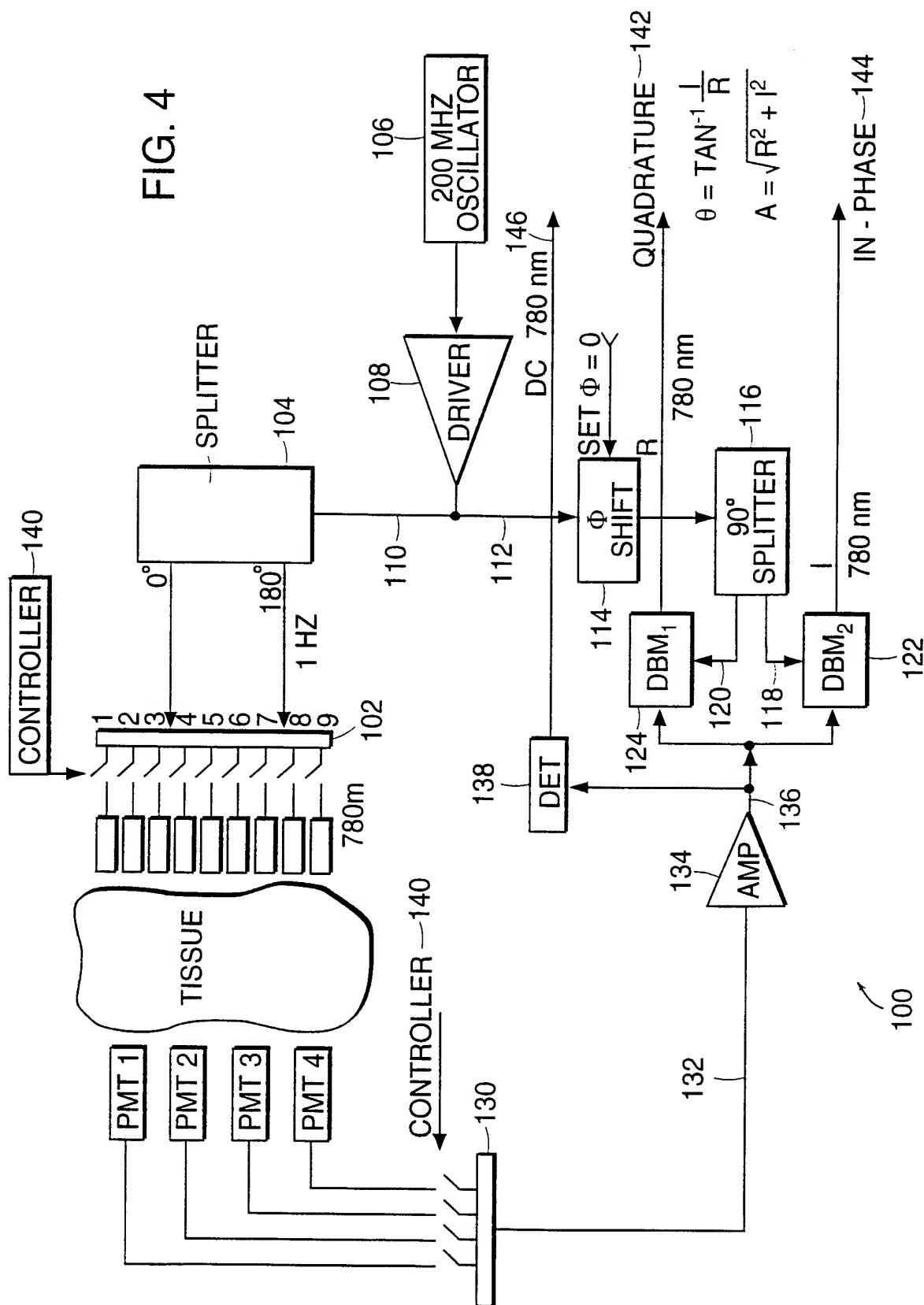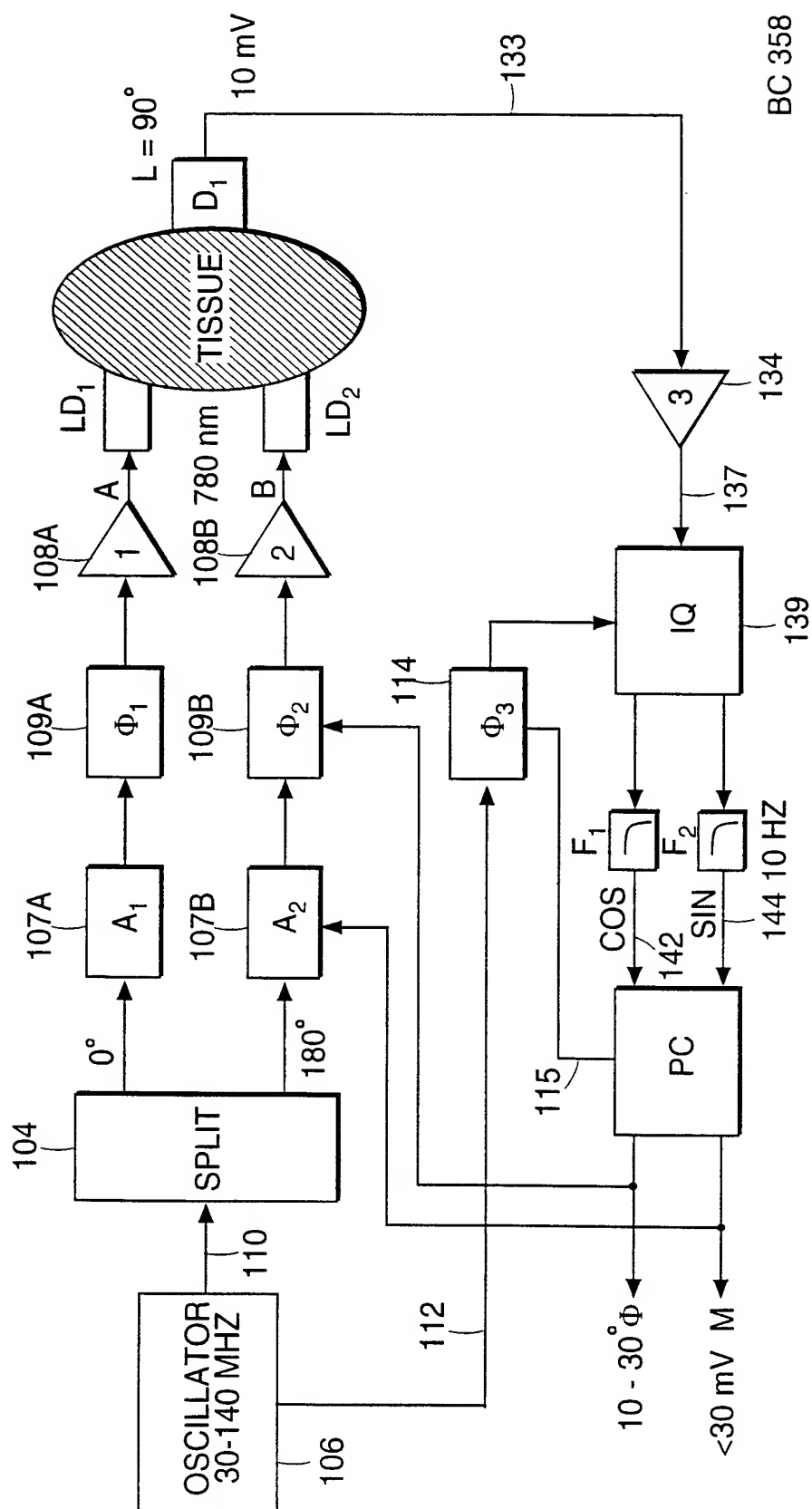
FIG. 4A

HOMODYNE PHASE CANCELLATION IMAGER
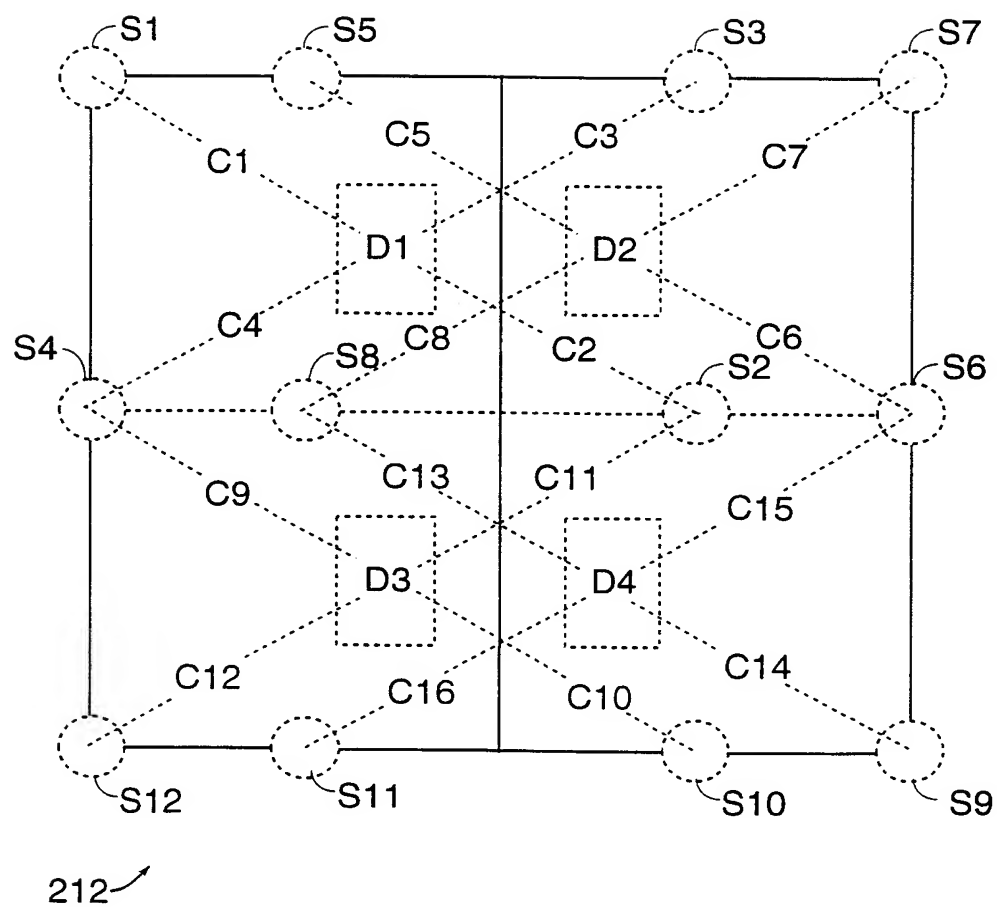(ONE 2S ID PART OF IMAGER)

FIG. 5

FIG. 6

FIG. 6A

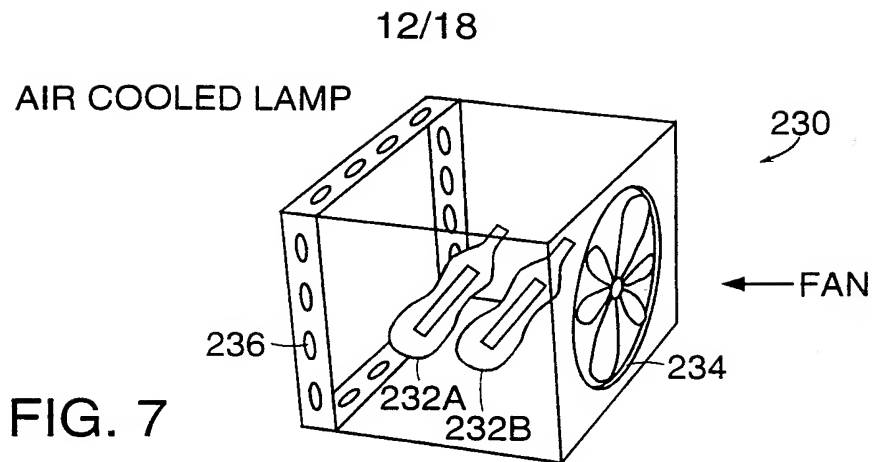AIR COOLED LAMP

230

FAN

236

232A

232B

234

FIG. 7
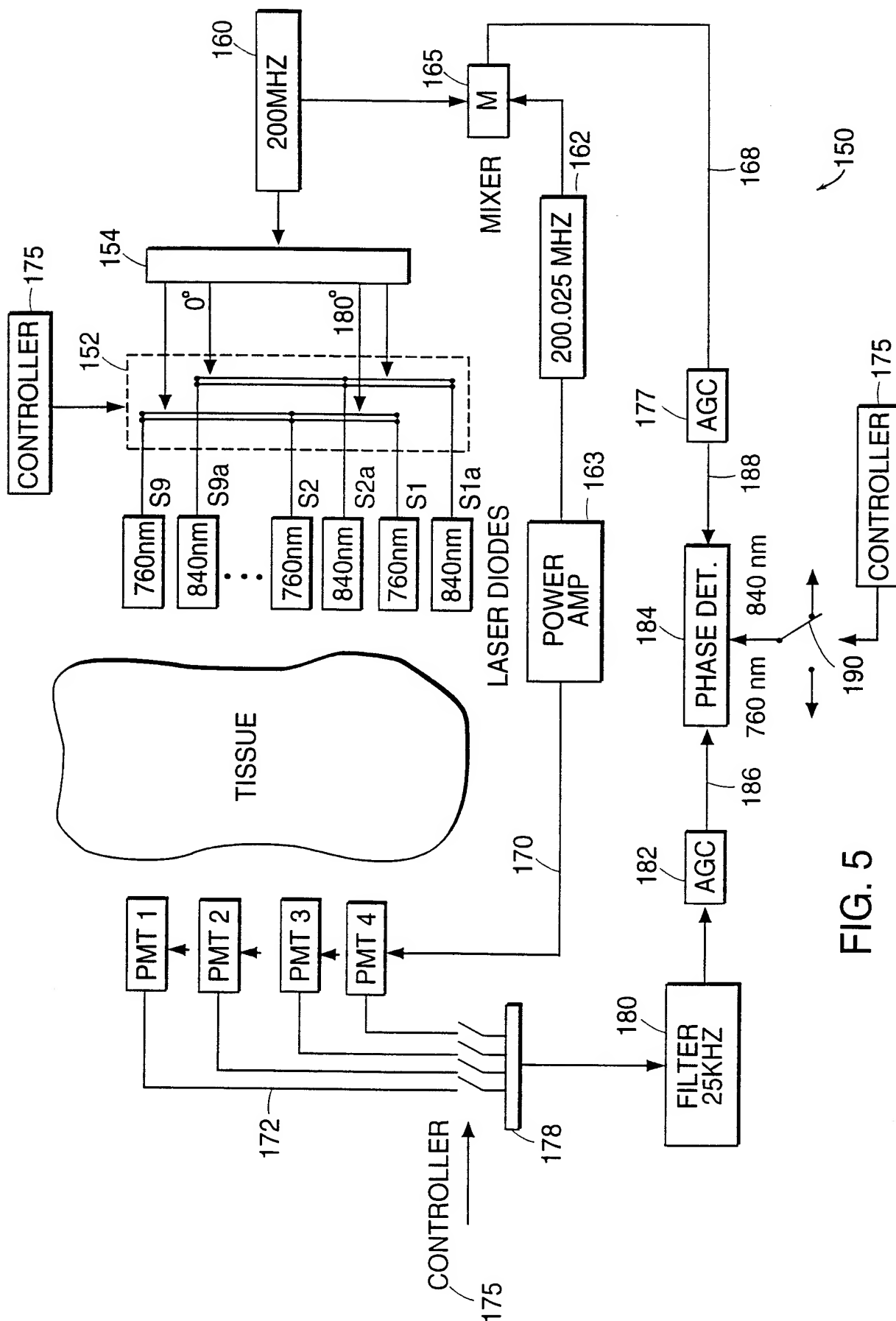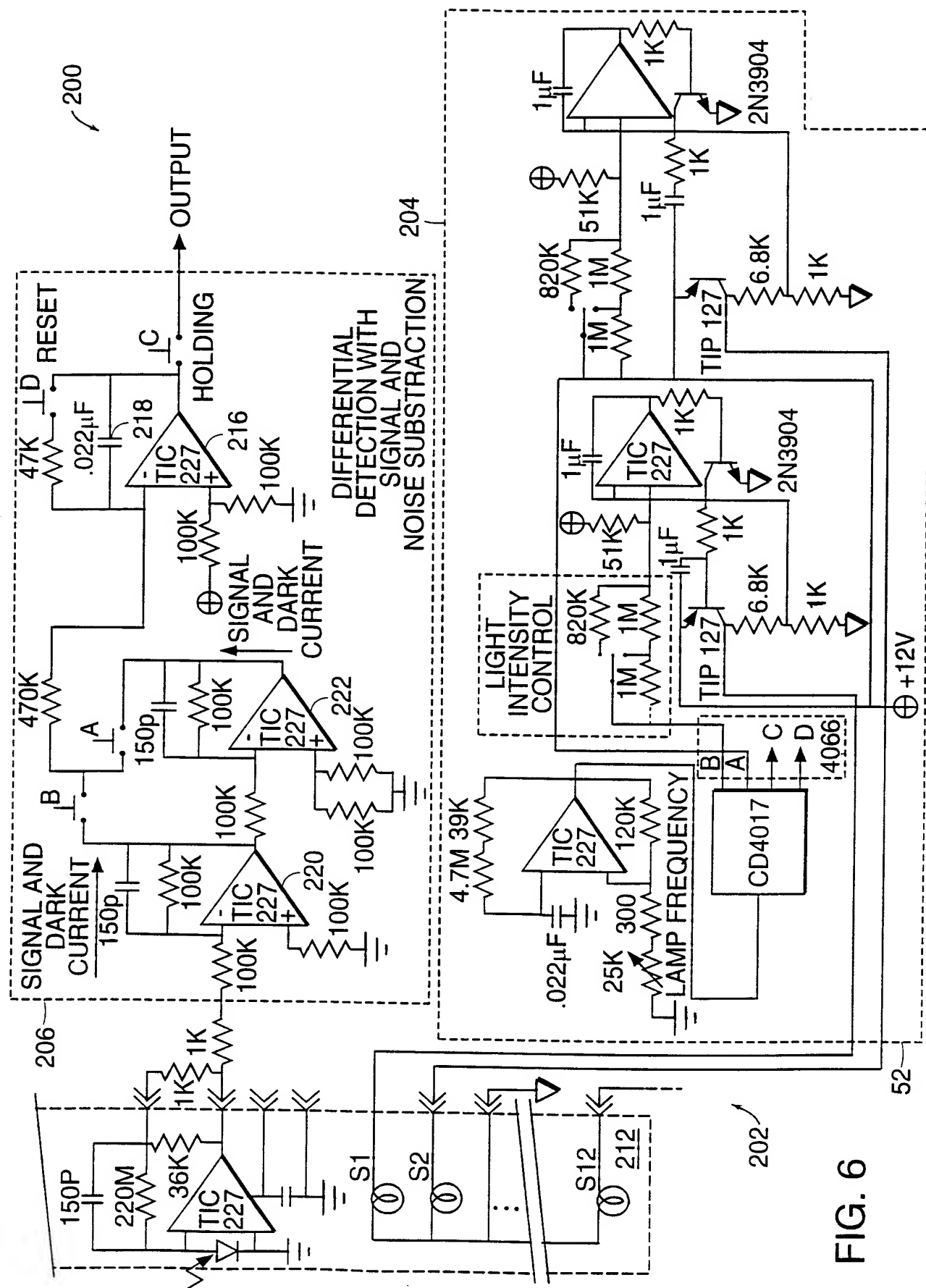
AIR COOLED LIGHT GUIDE

FIBER
COUPLING

242

240

248

AIR
INLET

FIG. 7A

INFLOWING
JETS

244

246

AIR IN
252B

AIR COOLED BARRIER

LIGHT SOURCE
254

AIR IN
252A

250

HOLLOW
BARRIER

FIG. 7B

252
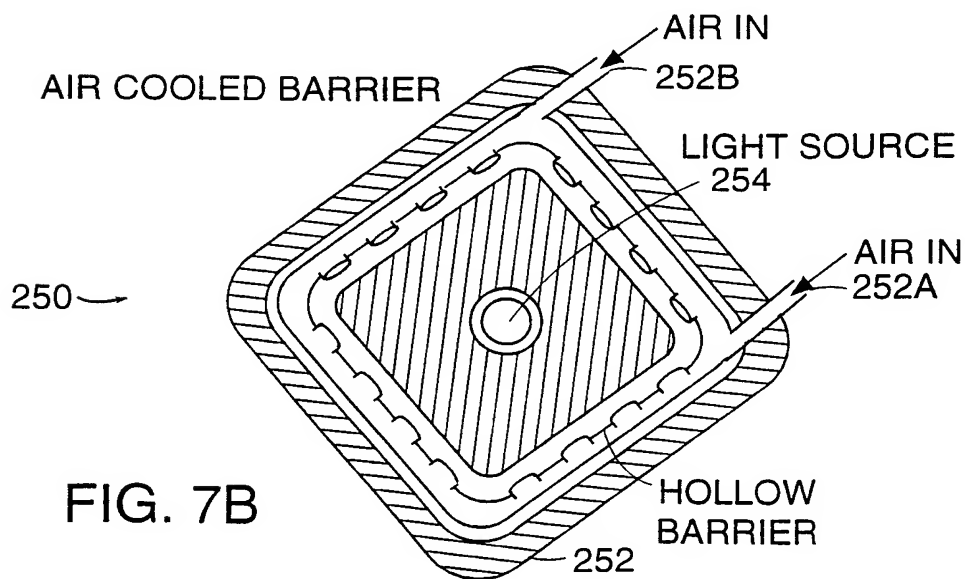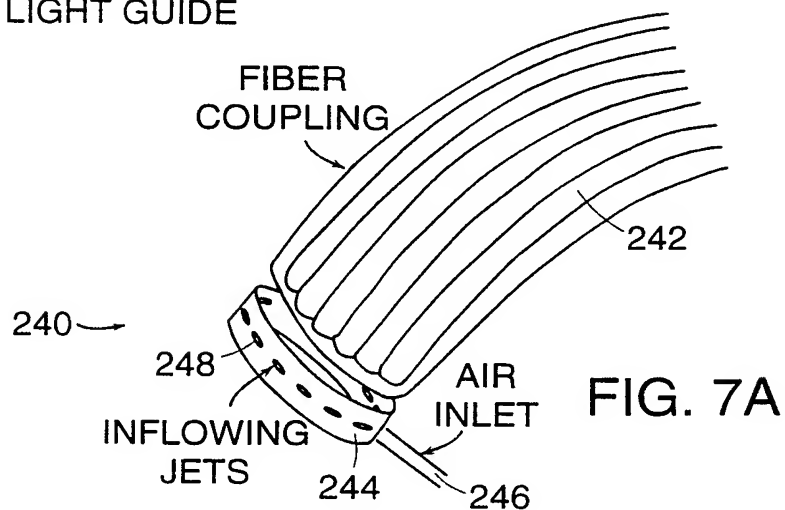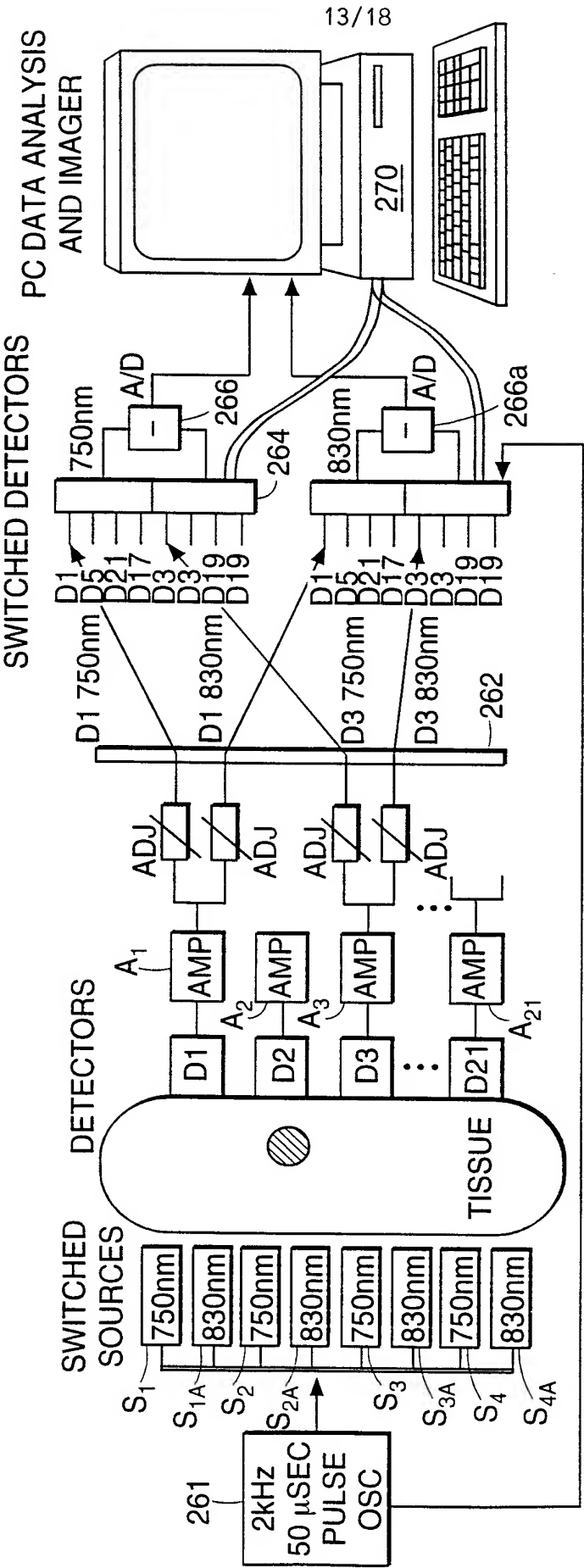
FIG. 8

CIRCUIT CONFIGURATION FOR
TIME MULTIPLEX APLITUDE CANCELLATION IMAGER

ONE ELEMENT
OF AMPLITUDE
CANCELLATION IMAGER

S_1, S_2 754nm
S_{1A}, S_{2A} 830nm
G_{1-4} 500μSEC GATE

FIG. 8A

272

TIME SEQUENCE S_1,S_1

FIG. 8B

TIME MULTIPLEX
4 X 2 SOURCES, 21 DETECTORS, SH, AGC
SAMPLE/HOLD/FILTER

FIG. 8C

FREQUENCY MULTIPLEX
21 X 2 SOURCES/OSCILLATORS, 4 DETECTORS, 40 FILTERS (HIGH/LOW), 20 AGC, 20 LOCK-IN

FIG. 8D

DUAL WAVELENGTH NIR PHASED ARRAY IMAGER
2D VASCULOGENESIS VS HYPERMETABOLISM IMAGERY
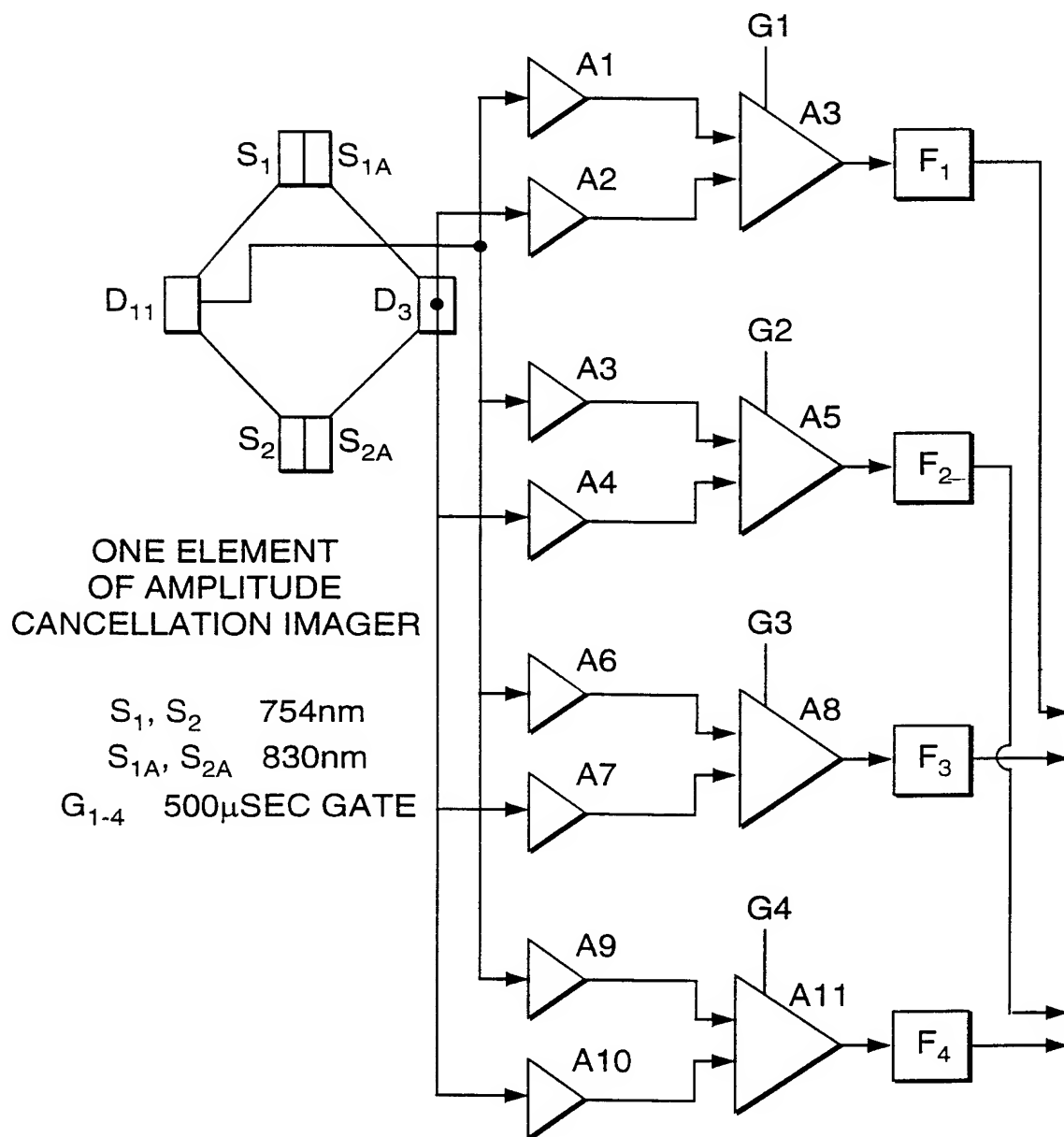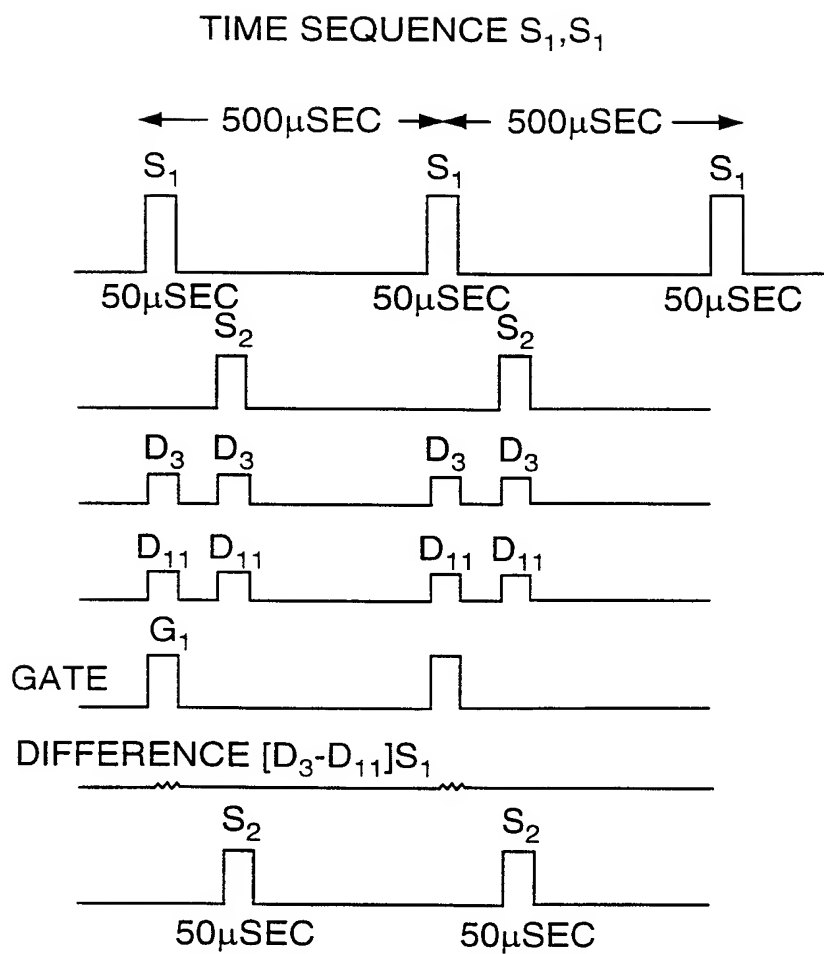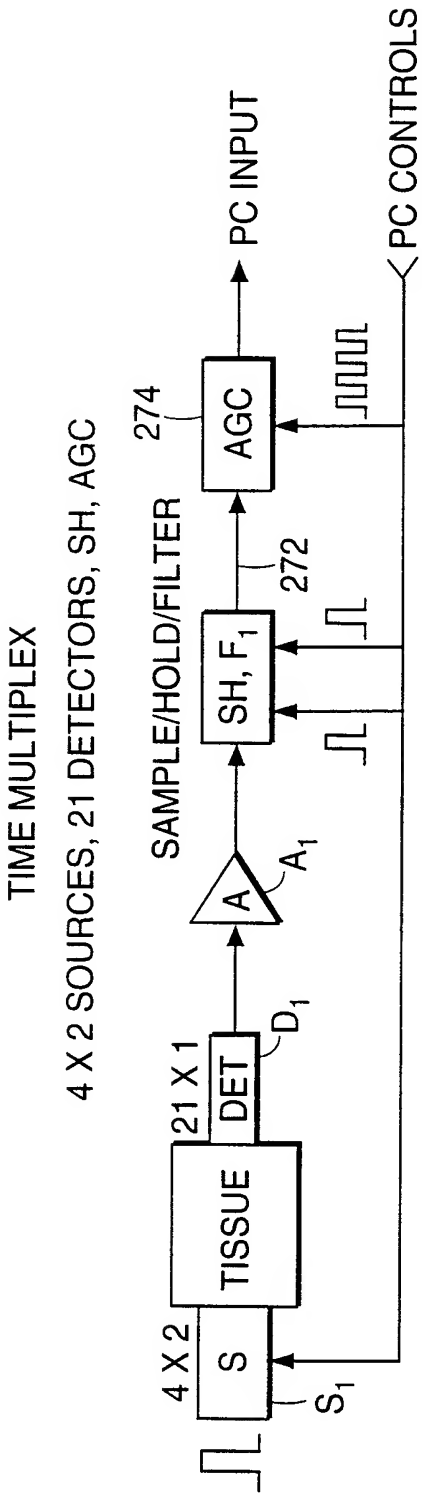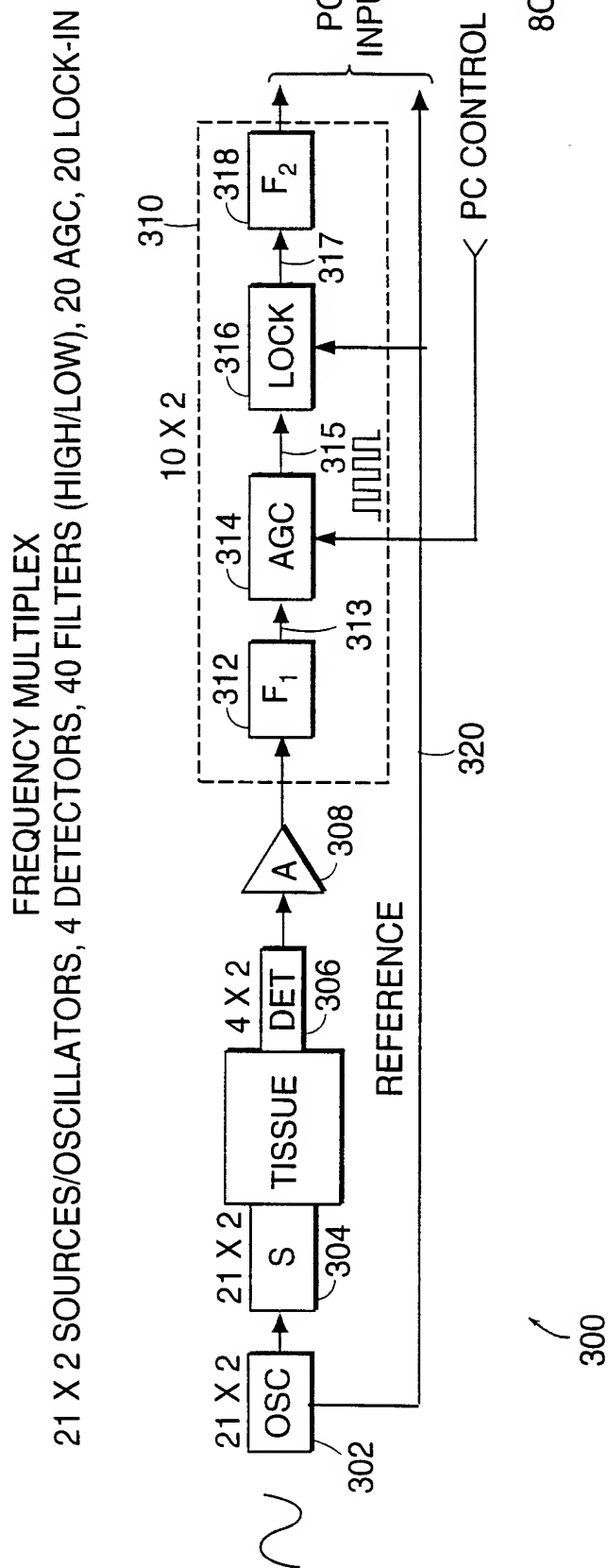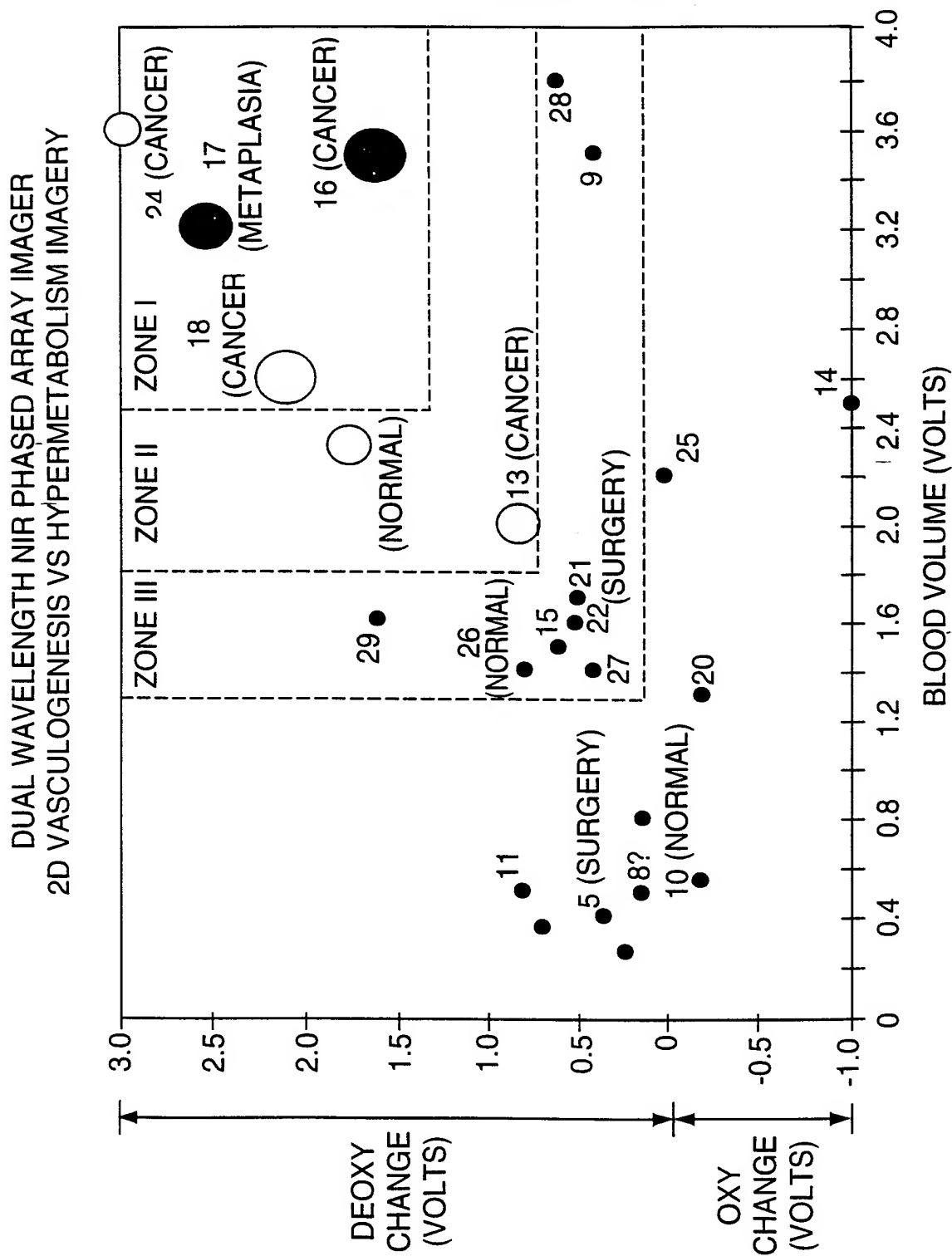
FIG. 9

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/03066

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6)   :A61B 5/00
US CL   :600/310.3 23, 324, 328, 340, 443, 473, 475-477, 479
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :   600/310, 323, 324, 326, 328, 333, 338, 340, 443, 473, 475-477, 479

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	US 5,853,370 A (CHANCE et al) 29 December 1998, entire document.	22, 23, 27-30, 32-36, 38-43 ---------------- 1-21, 24-30, 32-36, 38-42
Y	US 5,137,355 A (BARBOUR et al) 11 August 1992, col. 3 lines 41-46, and Abstract.	1-21
Y,P	US 5,845,639 A (HOCHMAN et al) 08 December 1998, Abstract.	24-30, 32-36, 38-42

☐ Further documents are listed in the continuation of Box C.   ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance		
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed	"&"	document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 MAY 1999	**2 7 MAY 1999**

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	RUTH S. SMITH
Facsimile No. (703) 305-3230	Telephone No. (703) 308-3063

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

INTERNATIONAL SEARCH REPORT	International application No. PCT/US99/03066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 31, 37
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest   ☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet(1))(July 1992)★